

2014

2015

BNF^{for} children

The authority on the
selection and use of
medicines in children

bnf.org

July 2014 – July 2015

Medicines information services

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

England

Birmingham	(0121) 424 7298
Bristol	(0117) 342 2867
Ipswich	(01473) 704 431
Leeds	(0113) 206 5377
Leicester	(0116) 255 5779
Liverpool	(0151) 794 8113/4/5/7 (0151) 794 8206

London

Guy's Hospital	(020) 7188 8750 (020) 7188 3849 (020) 7188 3855
Northwick Park Hospital	(020) 8869 2761 (020) 8869 3973
Newcastle	(0191) 282 4631
Southampton	(023) 8120 6908/9

Wales

Cardiff	(029) 2074 2979 (029) 2074 2251
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Scotland

Aberdeen	(01224) 552 316
Dundee	(01382) 632 351 (01382) 660 111 Extn 32351
Edinburgh	(0131) 242 2920
Glasgow	(0141) 211 4407

Northern Ireland

Belfast	(028) 9063 2032 (028) 9063 3847
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Republic of Ireland

Dublin	Dublin 473 0589 Dublin 453 7941 Extn 2348
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UK Teratology Information Service

Information on drug and chemical exposures in pregnancy 0844 892 0909

Medicines for Children information leaflets

Medicines information for parents and carers.
www.medicinesforchildren.org.uk

Patient Information Lines

NHS Direct 0845 4647

Poisons Information Services

UK National Poisons Information Service 0844 892 0111

Travel Immunisation

Up-to-date information on travel immunisation requirements may be obtained from:

National Travel Health Network and Centre (for healthcare professionals only) 0845 602 6712 (09.00–12.00 and 14.00–16.30 hours weekdays)

Travel Medicine Team, Health Protection Scotland (0141) 300 1130 (14.00–16.00 hours weekdays)

www.travax.nhs.uk (for registered users of the NHS website Travax only)

Welsh Assembly Government (029) 2082 1318 (09.00–17.30 hours weekdays)

Department of Health and Social Services (Belfast) (028) 9052 2118 (weekdays)

Information on drug therapy relating to dental treatment can be obtained by telephoning:

Liverpool (0151) 794 8206

Sport

Information on substances currently permitted or prohibited is provided in a card supplied by UK Anti-Doping.

Further information regarding medicines in sport is available from: www.ukad.org.uk

Tel: (020) 7766 7350

information@ukad.org.uk

United Kingdom Medicines Information Pharmacists Group (UKMIPG) website

www.ukmi.nhs.uk

Telephone numbers and email addresses of manufacturers listed in BNF Publications are shown in the Index of Manufacturers

BNF for children 2014–2015

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Email: direct@macmillan.co.uk

www.pharmpress.com

For all bulk orders of more than 20 copies:

Email: pharmpress@rpharms.com

Tel: +44 (0) 207 572 2266

BNFC is available online through bnf.org and MedicinesComplete, and as mobile apps; a PDA version is also available. In addition, BNFC content can be integrated into a local formulary by using BNFC on Formulary-Complete; see bnf.org for details.

BNFC is also available on www.evidence.nhs.uk and the NICE BNFC smartphone app can be downloaded with a NHS Athens password in England, Scotland, and Wales; for technical support, email: contactus@evidence.nhs.uk.

Distribution of printed BNFCs

In **England**, NICE purchases print editions of BNFC for distribution within the NHS. For details of who is eligible to receive a copy and further contact details, please refer to the NICE website: www.nice.org.uk/mpc/BritishNationalFormulary.jsp.

In **Scotland**, email:

nss.psd-bnf@nhs.net

In **Wales**, contact NHS Wales Shared Services Partnership—Contractor Services:

Tel: 01792 607 420

In **Northern Ireland**, email:

ni.bnf@hscni.net

The *BNF for Children* is for rapid reference by UK health professionals engaged in prescribing, dispensing, and administering medicines to children.

BNF for Children has been constructed using robust procedures for gathering, assessing and assimilating information on paediatric drug treatment, but may not always include all the information necessary for prescribing and dispensing. It is expected that the reader will be relying on appropriate professional knowledge and expertise to interpret the contents in the context of the circumstances of the individual child. *BNF for Children* should be used in conjunction with other appropriate and up-to-date literature and, where necessary, supplemented by expert advice. Information is also available from Medicines Information Services (see inside front cover).

Special care is required in managing childhood conditions with unlicensed medicines or with licensed medicines for unlicensed uses. Responsibility for the appropriate use of medicines lies solely with the individual health professional.

The print edition of *BNF for Children* is updated in July each year. For the most up-to-date information, please visit bnf.org which is updated monthly.

Pharmaid

Numerous requests have been received from developing countries for BNFCs. The Pharmaid scheme of the Commonwealth Pharmacists Association will dispatch old BNFCs to Commonwealth countries. BNFCs will be collected from certain community pharmacies in November. For further details check the health press or email: admin@commonwealthpharmacy.org

Contents

Preface	iv
Acknowledgements	v
BNF Staff	vi
How <i>BNF for Children</i> is constructed	ix
How to use <i>BNF for Children</i>	xi
Changes for this edition	xvii
General guidance	1
Prescription writing.....	4
Supply of medicines	6
Emergency supply of medicines	7
Prescribing Controlled Drugs.....	8
Adverse reactions to drugs	11
Prescribing in hepatic impairment.....	13
Prescribing in renal impairment	13
Prescribing in pregnancy.....	15
Prescribing in breast-feeding	15
Prescribing in palliative care	16
Prescribing in dental practice.....	21
Drugs and sport.....	22
Emergency treatment of poisoning	23
Notes on drugs and Preparations	
1: Gastro-intestinal system	34
2: Cardiovascular system	72
3: Respiratory system	131
4: Central nervous system	168
5: Infections	246
6: Endocrine system	355
7: Obstetrics, gynaecology, and urinary-tract disorders	398
8: Malignant disease and immunosuppression	419
9: Nutrition and blood	448
10: Musculoskeletal and joint diseases	504
11: Eye	523
12: Ear, nose, and oropharynx	541
13: Skin	556
14: Immunological products and vaccines	604
15: Anaesthesia	634
Appendices and indices	
Appendix 1: Interactions	660
Appendix 2: Borderline substances	771
Appendix 3: Cautionary and advisory labels for dispensed medicines	820
Appendix 4: Intravenous infusions for neonatal intensive care	823
Dental Practitioners' Formulary	826
Nurse Prescribers' Formulary	828
Non-medical prescribing	830
Index of manufacturers	831
Index	842
Medical emergencies in the community.....	Inside back cover

Preface

BNF for Children aims to provide prescribers, pharmacists, and other healthcare professionals with sound up-to-date information on the use of medicines for treating children.

A joint publication of the British Medical Association, the Royal Pharmaceutical Society, the Royal College of Paediatrics and Child Health, and the Neonatal and Paediatric Pharmacists Group, *BNF for Children* ('BNFC') is published under the authority of a Paediatric Formulary Committee which comprises representatives of these bodies, the Department of Health for England, and the Medicines and Healthcare products Regulatory Agency.

Many areas of paediatric practice have suffered from inadequate information on effective medicines. BNFC addresses this significant knowledge gap by providing practical information on the use of medicines in children of all ages from birth to adolescence. Information in BNFC has been validated against emerging evidence, best-practice guidelines, and crucially, advice from a network of clinical experts.

Drawing information from manufacturers' literature where appropriate, BNFC also includes a great deal of advice that goes beyond marketing authorisations (product licences). This is necessary because licensed indications frequently do not cover the clinical needs of children; in some cases, products for use in children need to be specially manufactured or imported. Careful consideration has been given to establishing the clinical need for unlicensed interventions with respect to the evidence and experience of their safety and efficacy; local paediatric formularies, clinical literature and national information resources have been invaluable in this process.

BNFC has been designed for rapid reference and the information presented has been carefully selected to aid decisions on prescribing, dispensing and administration of medicines. Less detail is given on areas such as malignant disease and the very specialist use of medicines generally undertaken in tertiary centres. BNFC should be interpreted in the light of professional knowledge and it should be supplemented as necessary by specialised publications. Information is also available from Medicines Information Services (see inside front cover).

It is **important** to use the most recent BNFC information for making clinical decisions. The print edition of *BNF for Children* is updated in July each year. Monthly updates are provided online via the BNF Publications website bnf.org, MedicinesComplete, and the NHS Evidence portal. The more important changes for this edition are listed on p. xvii; changes listed online are cumulative (from one print edition to the next), and can be printed off each month to show the main changes since the last print edition as an aide memoire for those using print copies.

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

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

British National Formulary,
Royal Pharmaceutical Society,
1 Lambeth High Street, London SE1 7JN.
editor@bnf.org

The contact email for manufacturers or pharmaceutical companies wishing to contact BNF Publications is manufacturerinfo@bnf.org

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How *BNF for Children* is constructed

BNF for Children (BNFC) is unique in bringing together authoritative, independent guidance on best practice with clinically validated drug information, enabling healthcare professionals to select safe and effective medicines for individual children.

Information in BNFC has been validated against emerging evidence, best-practice guidelines, and advice from a network of clinical experts. BNFC includes a great deal of advice that goes beyond marketing authorisations (product licences or summaries of product characteristics). This is necessary because licensed indications frequently do not cover the clinical needs of children; in some cases, products for use in children need to be specially manufactured or imported. Careful consideration has been given to establishing the clinical need for unlicensed interventions with respect to the evidence and experience of their safety and efficacy.

Hundreds of changes are made between print editions, and are published monthly online. The most clinically significant changes are listed at the front of each edition (p. xvii).

Paediatric Formulary Committee

The Paediatric Formulary Committee (PFC) is responsible for the content of BNFC. The PFC includes a neonatologist and paediatricians appointed by the Royal College of Paediatrics and Child Health, paediatric pharmacists appointed by the Royal Pharmaceutical Society and the Neonatal and Paediatric Pharmacists Group, doctors appointed by the BMJ Group, a GP appointed by the Royal College of General Practitioners, and representatives from the Medicines and Healthcare products Regulatory Agency (MHRA) and the Department of Health for England. The PFC decides on matters of policy and reviews amendments to BNFC in the light of new evidence and expert advice.

Dental Advisory Group

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

Editorial team

BNFC clinical writers have all worked as pharmacists and have a sound understanding of how drugs are used in clinical practice, including paediatrics. Each clinical writer is responsible for editing, maintaining, and updating specific chapters of BNFC. During the publication cycle the clinical writers review information in BNFC against a variety of sources (see below).

Amendments to the text are drafted when the clinical writers are satisfied that any new information is reliable and relevant. The draft amendments are passed to expert advisers for comment and then presented to the Paediatric Formulary Committee for consideration. Additionally, sections are regularly chosen from every chapter for thorough review. These planned reviews aim to verify all the information in the selected sections

and to draft any amendments to reflect current best practice.

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

Expert advisers

BNFC uses about 80 expert clinical advisers (including doctors, pharmacists, nurses, and dentists) throughout the UK to help with the clinical content. The role of these expert advisers is to review existing text and to comment on amendments drafted by the clinical writers. These clinical experts help to ensure that BNFC remains reliable by:

- commenting on the relevance of the text in the context of best clinical practice in the UK;
- checking draft amendments for appropriate interpretation of any new evidence;
- providing expert opinion in areas of controversy or when reliable evidence is lacking;
- advising on areas where BNFC diverges from summaries of product characteristics;
- advising on the use of unlicensed medicines or of licensed medicines for unlicensed uses ('off-label' use);
- providing independent advice on drug interactions, prescribing in hepatic impairment, renal impairment, pregnancy, breast-feeding, neonatal care, palliative care, and the emergency treatment of poisoning.

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

BNFC also works closely with a number of expert bodies that produce clinical guidelines. Drafts or pre-publication copies of guidelines are routinely received for comment and for assimilation into BNFC.

Sources of BNFC information

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

Summaries of product characteristics BNFC receives summaries of product characteristics (SPCs) of all new products as well as revised SPCs for existing products. The SPCs are a key source of product information and are carefully processed, despite the ever-increasing volume of information being issued by the pharmaceutical industry. Such processing involves:

- verifying the approved names of all relevant ingredients including 'non-active' ingredients (BNFC is committed to using approved names and descriptions as laid down by the Human Medicines Regulations 2012);
- comparing the indications, cautions, contra-indications, and side-effects with similar existing drugs. Where these are different from the expected pattern, justification is sought for their inclusion or exclusion;
- seeking independent data on the use of drugs in pregnancy and breast-feeding;

- incorporating the information into BNFC using established criteria for the presentation and inclusion of the data;
- checking interpretation of the information by a second clinical writer before submitting to a lead editor; changes relating to doses receive an extra check;
- identifying potential clinical problems or omissions and seeking further information from manufacturers or from expert advisers;
- careful validation of any areas of divergence of BNFC from the SPC before discussion by the Committee (in the light of supporting evidence);
- constructing, with the help of expert advisers, a comment on the role of the drug in the context of similar drugs. Much of this processing is applicable to the following sources as well.

Expert advisers The role of expert clinical advisers in providing the appropriate clinical context for all BNFC information is discussed above.

Literature Clinical writers monitor core medical, paediatric, and pharmaceutical journals. Research papers and reviews relating to drug therapy are carefully processed. When a difference between the advice in BNFC and the paper is noted, the new information is assessed for reliability and relevance to UK clinical practice. If necessary, new text is drafted and discussed with expert advisers and the Paediatric Formulary Committee. BNFC enjoys a close working relationship with a number of national information providers.

Systematic reviews BNFC has access to various databases of systematic reviews (including the Cochrane Library and various web-based resources). These are used for answering specific queries, for reviewing existing text, and for constructing new text. Clinical writers receive training in critical appraisal, literature evaluation, and search strategies. Reviews published in Clinical Evidence are used to validate BNFC advice.

Consensus guidelines The advice in BNFC is checked against consensus guidelines produced by expert bodies. A number of bodies make drafts or pre-publication copies of the guidelines available to BNFC; it is therefore possible to ensure that a consistent message is disseminated. BNFC routinely processes guidelines from the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), and the Scottish Intercollegiate Guidelines Network (SIGN).

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

Statutory information BNFC routinely processes relevant information from various Government bodies including Statutory Instruments and regulations affecting the Prescription only Medicines Order. Official

compendia such as the British Pharmacopoeia and its addenda are processed routinely to ensure that BNFC complies with the relevant sections of the Human Medicines Regulations 2012.

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

Relevant professional statements issued by the Royal Pharmaceutical Society are included in BNFC as are guidelines from bodies such as the Royal College of Paediatrics and Child Health.

BNFC reflects information from the Drug Tariff, the Scottish Drug Tariff, and the Northern Ireland Drug Tariff.

Pricing information NHS Prescription Services (from the NHS Business Services Authority) provides information on prices of medicinal products and appliances in BNFC.

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

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

Virtual user groups BNFC has set up virtual user groups across various healthcare professions (e.g. doctors, pharmacists, nurses). The aim of these groups will be to provide feedback to the editors and publishers to ensure that BNF publications continue to serve the needs of its users.

Market research Market research is conducted at regular intervals to gather feedback on specific areas of development, such as drug interactions or changes to the way information is presented in digital formats.

BNFC is an independent professional publication that is kept up-to-date and addresses the day-to-day prescribing information needs of healthcare professionals treating children. Use of this resource throughout the health service helps to ensure that medicines are used safely, effectively, and appropriately in children.

How to use *BNF for Children*

BNF for Children (BNFC) provides information on the use of medicines in children ranging from neonates (including preterm neonates) to adolescents. The terms infant, child, and adolescent are not used consistently in the literature; to avoid ambiguity actual ages are used in the dose statements in BNFC. The term neonate is used to describe a newborn infant aged 0–28 days. The terms child or children are used generically to describe the entire range from infant to adolescent in BNFC.

In order to achieve the safe, effective, and appropriate use of medicines in children, healthcare professionals must be able to use BNFC effectively, and keep up to date with significant changes in BNFC that are relevant to their clinical practice. *How to Use BNF for Children* is aimed as a quick refresher for all healthcare professionals involved with prescribing, monitoring, supplying, and administering medicines for children, and as a learning aid for students training to join these professions. While *How to Use BNF for Children* is linked to the main elements of rational prescribing, the generic structure of this section means that it can be adapted for teaching and learning in different clinical settings.

Structure of BNFC

The Contents list (on p. iii) shows that information in BNFC is divided into:

- *How BNF for Children is Constructed* (p. ix);
- *Changes* (p. xvii);
- *General Guidance* (p. 1), which provides practical information on many aspects of prescribing from writing a prescription to prescribing in palliative care;
- *Emergency Treatment of Poisoning* (p. 23), which provides an overview on the management of acute poisoning;
- *Classified notes on clinical conditions, drugs, and preparations*, these notes are divided into 15 chapters, each of which is related to a particular system of the body (e.g. chapter 3, Respiratory System) or to an aspect of paediatric care (e.g. chapter 5, Infections). Each chapter is further divided into classified sections. Each section usually begins with *prescribing notes* followed by relevant drug *monographs* and *preparations* (see fig. 1). Drugs are classified in a section according to their pharmacology and therapeutic use;
- *Appendices and Indices*, includes 4 Appendices (providing information on drug interactions, borderline substances, cautionary and advisory labels for dispensed medicines, and intravenous infusions for neonatal intensive care), the Dental Practitioners' Formulary, the Nurse Prescribers' Formulary, Non-medical Prescribing, Index of Manufacturers, and the main Index. The information in the Appendices should be used in conjunction with relevant information in the chapters.

Finding information in BNFC

BNFC includes a number of aids to help access relevant information:

- *Index*, where entries are included in alphabetical order of non-proprietary drug names, proprietary drug names, clinical conditions, and prescribing topics. A specific entry for 'Dental Prescribing' brings together topics of relevance to dentists. The page reference to the drug monograph is shown in **bold** type. References to drugs in Appendices 1 and 3 are not included in the main Index;
- *Contents* (p. iii), provides a hierarchy of how information in BNFC is organised;
- The beginning of each chapter includes a *classified hierarchy* of how information is organised in that chapter;
- *Running heads*, located next to the page number on the top of each page, show the section of BNFC that is being used;
- *Thumbnails*, on the outer edge of each page, show the chapter of BNFC that is being used;
- *Cross-references*, lead to additional relevant information in other parts of BNFC.

Finding dental information in BNFC

Extra signposts have been added to help access dental information in BNFC:

- *Prescribing in Dental Practice* (p. 21), includes a contents list dedicated to drugs and topics of relevance to dentists, together with cross-references to the prescribing notes in the appropriate sections of BNFC. For example, a review of this list shows that information on the local treatment of oral infections is located in chapter 12 (Ear, Nose, and Oropharynx) while information on the systemic treatment of these infections is found in chapter 5 (Infections). Further guidance for dental practice can be found in the BNF.
- *Side-headings*, in the prescribing notes, side-headings facilitate the identification of advice on oral conditions (e.g. Dental and Orofacial Pain, p. 199);
- *Dental prescribing on NHS*, in the body of BNFC, preparations that can be prescribed using NHS form FP10D (GP14 in Scotland, WP10D in Wales) can be identified by means of a note headed 'Dental prescribing on NHS' (e.g. Aciclovir Oral Suspension, p. 327).

Identifying effective drug treatments

The prescribing notes in BNFC provide an overview of the drug management of common conditions and facilitate rapid appraisal of treatment options (e.g. epilepsy, p. 216). For ease of use, information on the management of certain conditions has been tabulated (e.g. acute asthma, p. 134).

Advice issued by the National Institute for Health and Clinical Excellence (NICE) is integrated within BNFC prescribing notes if appropriate. Summaries of NICE technology appraisals, and relevant short guidelines, are included in pink panels. BNFC also includes advice issued by the Scottish Medicines Consortium (SMC)

when a medicine is restricted or not recommended for use within NHS Scotland.

In order to select safe and effective medicines for individual children, information in the prescribing notes must be used in conjunction with other prescribing details about the drugs and knowledge of the child's medical and drug history.

A brief description of the clinical uses of a drug can usually be found in the Indication and Dose section of its monograph (e.g. ibuprofen, p. 508); a cross-reference is provided to any indications for that drug that are covered in other sections of BNFC.














The symbol  is used to denote preparations that are considered to be less suitable for prescribing. Although

Figure 1 Illustrates the typical layout of a drug monograph and preparation records in BNFC

<div style="border: 1px solid black; padding: 5px;"> <div style="background-color: #f0f0f0; padding: 5px; border-bottom: 1px solid black;">  DRUG NAME  </div> <div style="padding: 5px;"> <p>Cautions details of precautions required and also any monitoring required</p> <p>Counselling Verbal explanation to the patient of specific details of the drug treatment (e.g. posture when taking a medicine)</p> <p>Contra-indications circumstances when a drug should be avoided</p> <p>Hepatic impairment advice on the use of a drug in hepatic impairment</p> <p>Renal impairment advice on the use of a drug in renal impairment</p> <p>Pregnancy advice on the use of a drug during pregnancy</p> <p>Breast-feeding advice on the use of a drug during breast-feeding</p> <p>Side-effects very common (greater than 1 in 10) and common (1 in 100 to 1 in 10); <i>less commonly</i> (1 in 1000 to 1 in 100); <i>rarely</i> (1 in 10 000 to 1 in 1000); <i>very rarely</i> (less than 1 in 10 000); also reported, frequency not known</p> <p>Licensed use shows if a drug unlicensed in the UK, or 'off-label' use of drug licensed in the UK</p> <p>Indication and dose</p> <p style="padding-left: 20px;">Details of uses and indications</p> <ul style="list-style-type: none"> ● By route <p style="padding-left: 20px;">Child dose and frequency of administration (max. dose) for specific age group</p> <ul style="list-style-type: none"> ● By alternative route <p style="padding-left: 20px;">Child dose and frequency</p> <p>Administration practical advice on the administration of a drug</p> <p>Approved Name (Non-proprietary)  ←</p> <p style="padding-left: 20px;">Pharmaceutical form, sugar-free, active ingredient mg/mL, net price, pack size = basic NHS price. Label: (as in Appendix 3)</p> <p>1. Exceptions to the prescribing status are indicated by a note or footnote.</p> <p>Proprietary Name (Manufacturer)   ←</p> <p style="padding-left: 20px;">Pharmaceutical form, colour, coating, active ingredient and amount in dosage form, net price, pack size = basic NHS price. Label: (as in Appendix 3)</p> <p style="padding-left: 20px;">Excipients include clinically important excipients</p> <p style="padding-left: 20px;">Electrolytes clinically significant quantities of electrolytes</p> <p style="padding-left: 20px;">Note Specific notes about the product e.g. handling</p> </div> </div> <div style="vertical-align: top; padding-left: 20px;"> <p>In the case of compound preparations, the indications, cautions, contra-indications, side-effects and interactions of all constituents should be taken into account for prescribing.</p> <p>When no suitable licensed preparation is available, details of preparations that may be imported or formulations available as manufactured specials or extemporaneous preparations are included.</p> <p>Drugs</p> <p>Drugs appear under pharmacopoeial or other non-proprietary titles. When there is an <i>appropriate current monograph</i> (Human Medicines Regulations 2012) preference is given to a name at the head of that monograph; otherwise a British Approved Name (BAN), if available, is used.</p> <p>The symbol  is used to denote those preparations considered to be less suitable for prescribing. Although such preparations may not be considered as drugs of first choice, their use may be justifiable in certain circumstances.</p> <p>Prescription-only medicines </p> <p>This symbol has been placed against preparations that are available only on a prescription from an appropriate practitioner. For more detailed information see <i>Medicines, Ethics and Practice</i>, London, Pharmaceutical Press (always consult latest edition).</p> <p>The symbols     indicate that the preparations are subject to the prescription requirements of the Misuse of Drugs Act. For advice on prescribing such preparations see Prescribing Controlled Drugs.</p> <p>Preparations not available for NHS prescription </p> <p>This symbol has been placed against preparations that are not prescribable under the NHS. Those prescribable only for specific disorders have a footnote specifying the condition(s) for which the preparation remains available. Some preparations which are not <i>prescribable</i> by brand name under the NHS may nevertheless be <i>dispensed</i> using the brand name provided that the prescription shows an appropriate non-proprietary name.</p> <p>Prices</p> <p>Prices have been calculated from the basic cost used in pricing NHS prescriptions, see also Prices in BNFC.</p> </div>

Preparations

Preparations are included under a non-proprietary title, if they are marketed under such a title, if they are not otherwise prescribable under the NHS, or if they may be prepared extemporaneously.

such preparations may not be considered as drugs of first choice, their use may be justifiable in certain circumstances.

Drug management of medical emergencies

Guidance on the drug management of medical emergencies can be found in the relevant BNFC chapters (e.g. treatment of anaphylaxis is included in section 3.4.3). A summary of drug doses used for Medical Emergencies in the Community can be found in the glossy pages at the back of BNFC. Algorithms for New-born, Paediatric Basic, and Paediatric Advanced Life Support can also be found within these pages.

Minimising harm in children with co-morbidities

The drug chosen to treat a particular condition should have minimal detrimental effects on the child's other diseases and minimise the child's susceptibility to adverse effects. To achieve this, the *Cautions*, *Contra-indications*, and *Side-effects* of the relevant drug should be reviewed, and can usually be found in the drug monograph. However, if a class of drugs (e.g. tetracyclines, p. 277) share the same cautions, contra-indications, and side-effects, these are amalgamated in the prescribing notes while those unique to a particular drug in that class are included in its individual drug monograph. Occasionally, the cautions, contra-indications, and side-effects may be included within a preparation record if they are specific to that preparation or if the preparation is not accompanied by a monograph.

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

The impact that potential side-effects may have on a child's quality of life should also be assessed. For instance, in a child who has constipation, it may be preferable to avoid a drug that frequently causes constipation. The prescribing notes in BNFC may highlight important safety concerns and differences between drugs in their ability to cause certain side-effects.

Prescribing for children with hepatic or renal impairment

Drug selection should aim to minimise the potential for drug accumulation, adverse drug reactions, and exacerbation of pre-existing hepatic or renal disease. If it is necessary to prescribe drugs whose effect is altered by hepatic or renal disease, appropriate drug dose adjustments should be made, and the child should be monitored adequately. The general principles for prescribing are outlined under *Prescribing in Hepatic Impairment* (p. 13) and *Prescribing in Renal Impairment* (p. 13). Information about drugs that should be avoided or used with caution in hepatic disease or renal impairment can be found in drug monographs under *Hepatic Impairment* and *Renal Impairment* (e.g. fluconazole, p. 305). However, if a class of drugs (e.g. tetracyclines, p. 277) share

the same recommendations for use in hepatic disease or renal impairment, this advice is presented in the prescribing notes under *Hepatic Impairment* and *Renal Impairment* and any advice that is unique to a particular drug in that class is included in its individual drug monograph.

Prescribing for patients who are pregnant or breast-feeding

Drug selection should aim to minimise harm to the fetus, nursing infant, and mother. The infant should be monitored for potential side-effects of drugs used by the mother during pregnancy or breast-feeding. The general principles for prescribing are outlined under *Prescribing in Pregnancy* (p. 15) and *Prescribing in Breast-feeding* (p. 15). The prescribing notes in BNFC chapters provide guidance on the drug treatment of common conditions that can occur during pregnancy and breast-feeding (e.g. asthma, p. 131). Information about the use of specific drugs during pregnancy and breast-feeding can be found in their drug monographs under *Pregnancy* and *Breast-feeding* (e.g. fluconazole, p. 305). However, if a class of drugs (e.g. tetracyclines, p. 277) share the same recommendations for use during pregnancy or breast-feeding, this advice is amalgamated in the prescribing notes under *Pregnancy* and *Breast-feeding* while any advice that is unique to a particular drug in that class is included in its individual drug monograph.

Minimising drug interactions

Drug selection should aim to minimise drug interactions. If it is necessary to prescribe a potentially serious combination of drugs, children should be monitored appropriately. The mechanisms underlying drug interactions are explained in Appendix 1 (p. 660).

Details of drug interactions can be found in Appendix 1 of BNFC (p. 661). Drugs and their interactions are listed in alphabetical order of the non-proprietary drug name, and cross-references to drug classes are provided where appropriate. Each drug or drug class is listed twice: in the alphabetical list and also against the drug or class with which it interacts. The symbol ● is placed against interactions that are potentially serious and where combined administration of drugs should be avoided (or only undertaken with caution and appropriate monitoring). Interactions that have no symbol do not usually have serious consequences.

If a drug or drug class has interactions, a cross reference to where these can be found in Appendix 1 is provided under the *Cautions* of the drug monograph or prescribing notes.

Selecting the dose

The drug dose is usually located in pink panels within the *Indication* and *Dose* section of the drug monograph or within the *Dose* section of the preparation record. Doses are linked to specific indications and routes of administration. The dose of a drug may vary according to different indications, routes of administration, age, body-weight, and body-surface area. When the dose of a drug varies according to different indications, each indication and its accompanying dose is included in a separate pink panel (e.g. aciclovir, p. 326). The dose is located within the preparation record when the dose varies according to different formulations of that drug

(e.g. amphotericin, p. 309) or when a preparation has a dose different to that in its monograph. Occasionally, drug doses may be included in the prescribing notes for practical reasons (e.g. doses of drugs in *Helicobacter pylori* eradication regimens, p. 41). The right dose should be selected for the right age and body-weight (or body surface area) of the child, as well as for the right indication, route of administration, and preparation.

Doses in BNFC are usually assigned to specific age ranges; neonatal doses are preceded by the word **Neonate**, all other doses are preceded by the word **Child**. Age ranges in BNFC are described as shown in the following example:

Child 1 month–4 years refers to a child from 1 month old up to their 4th birthday;

Child 4–10 years refers to a child from the day of their 4th birthday up to their 10th birthday.

However, a pragmatic approach should be applied to these cut-off points depending on the child's physiological development, condition, and if weight is appropriate for the child's age.

For some drugs (e.g. vancomycin, p. 289) the neonatal dose varies according to the *corrected gestational age* of the neonate. Corrected gestational age is the neonate's total age expressed in weeks from the start of the mother's last menstrual period. For example, a 3 week old baby born at 27 weeks gestation is treated as having a corrected gestational age of 30 weeks. A term baby has a corrected gestational age of 37–42 weeks when born. For most other drugs, the dose can be based on the child's actual date of birth irrespective of corrected gestational age. However, the degree of prematurity, the maturity of renal and hepatic function, and the clinical properties of the drug need to be considered on an individual basis.

Many children's doses in BNFC are standardised by *body-weight*. To calculate the dose for a given child the weight-standardised dose is multiplied by the child's weight (or occasionally by the child's ideal weight for height). The calculated dose should not normally exceed the maximum recommended dose for an adult. For example, if the dose is 8 mg/kg (max. 300 mg), a child of 10 kg body-weight should receive 80 mg, but a child of 40 kg body-weight should receive 300 mg (rather than 320 mg). Calculation by body-weight in the overweight child may result in much higher doses being administered than necessary; in such cases, the dose should be calculated from an ideal weight for height.

Occasionally, some doses in BNFC are standardised by *body surface area* because many physiological phenomena correlate better with body surface area. In these cases, to calculate the dose for a given child, the body surface area-standardised dose is multiplied by the child's body surface area. The child's body surface area can be estimated from his or her weight using the tables for Body Surface Area in Children located in the glossy pages at the back of the print version of BNFC.

The doses of some drugs may need to be adjusted if their effects are altered by concomitant use with other drugs, or in patients with hepatic or renal impairment (see Minimising Drug Interactions, and Prescribing for Children with Hepatic or Renal Impairment).

Wherever possible, doses are expressed in terms of a definite frequency (e.g. if the dose is 1 mg/kg twice

daily, a child of body-weight 9 kg would receive 9 mg twice daily). Occasionally, it is necessary to include doses in the total daily dose format (e.g. 10 mg/kg daily in 3 divided doses); in these cases the total daily dose should be divided into individual doses (in this example a child of body-weight 9 kg would receive 30 mg 3 times daily).

Most drugs can be administered at slightly irregular intervals during the day. Some drugs, e.g. antimicrobials, are best given at regular intervals. Some flexibility should be allowed in children to avoid waking them during the night. For example, the night-time dose may be given at the child's bedtime.

Special care should be taken when converting doses from one metric unit to another, and when calculating infusion rates or the volume of a preparation to administer. Conversions for imperial to metric measures can be found in the glossy pages at the back of BNFC. Where possible, doses should be rounded to facilitate administration of suitable volumes of liquid preparations, or an appropriate strength of tablet or capsule.

Selecting a suitable preparation

Children should be prescribed a preparation that complements their daily routine, and that provides the right dose of drug for the right indication and route of administration.

In BNFC, preparations usually follow immediately after the monograph for the drug which is their main ingredient. The preparation record (see fig. 1) provides information on the type of formulation (e.g. tablet), the amount of active drug in a solid dosage form, and the concentration of active drug in a liquid dosage form. The legal status is shown for prescription only medicines and controlled drugs; any exception to the legal status is shown by a Note immediately after the preparation record or a footnote. If a proprietary preparation has a distinct colour, coating, scoring, or flavour, this is shown in the preparation record. If a proprietary preparation includes excipients usually specified in BNFC (see p. 2), these are shown in the *Excipients* statement, and if it contains clinically significant quantities of electrolytes, these are usually shown in the *Electrolytes* statement.

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

Where a drug has several preparations, those of a similar type may be grouped together under a heading (e.g. 'Modified-release' for theophylline preparations, p. 141). Where there is good evidence to show that the preparations for a particular drug are not interchangeable, this is stated in a Note either in the Dose section of the monograph or by the group of preparations affected. When the dose of a drug varies according to different formulations of that drug, the right dose should be prescribed for the preparation selected.

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

Unlicensed preparations that are available from 'Special order' manufacturers and specialist importing companies are included (e.g. betaine tablets, p. 500).

Writing prescriptions

Guidance is provided on writing prescriptions that will help to reduce medication errors, see p. 4. Prescription requirements for controlled drugs are also specified on p. 8.

Administering drugs

Basic information on the route of administration is provided in the Indication and Dose section of a drug monograph or the Dose section of a preparation record. Further details, such as masking the bitter taste of some medicines, may be provided in the *Administration* section of a drug monograph (e.g. proguanil, p. 345). Practical information is also provided on the preparation of intravenous drug infusions, including compatibility of drugs with standard intravenous infusion fluids, method of dilution or reconstitution, and administration rates (e.g. co-amoxiclav, p. 266). The *Administration* section is located within preparation records when this information varies according to different preparations of that drug (e.g. amphotericin, p. 309). If a class of drugs (e.g. topical corticosteroids, p. 566) share the same administration advice, this may be presented in the prescribing notes.

Whenever possible, intramuscular injections should be avoided in children because they are painful.

Information on intravenous infusions for neonatal intensive care can also be found in Appendix 4, p. 823.

Advising children (and carers)

The prescriber, the child's carer, and the child (if appropriate) should agree on the health outcomes desired and on the strategy for achieving them (see Taking Medicines to Best Effect, p. 1). Taking the time to explain to the child (and carers) the rationale and the potential adverse effects of treatment may improve adherence. For some medicines there is a special need for counselling (e.g. recognising signs of blood, liver, or skin disorders with carbamazepine); this is shown in *Counselling* statements, usually in the Cautions or Indication and Dose section of a monograph, or within a preparation record if it is specific to that preparation.

Children and their carers should be advised if treatment is likely to affect their ability to perform skilled tasks (e.g. driving).

Cautionary and advisory labels that pharmacists are recommended to add when dispensing are included in the preparation record (see fig. 1). Details of these labels can be found in Appendix 3 (p. 820).

Monitoring drug treatment

Children should be monitored to ensure they are achieving the expected benefits from drug treatment without any unwanted side-effects. The prescribing notes or the Cautions in the drug monograph specify any special monitoring requirements. Further information on mon-

itoring the plasma concentration of drugs with a narrow therapeutic index can be found in the Pharmacokinetics section or as a Note under the Dose section of the drug monograph.

Identifying and reporting adverse drug reactions

Clinically relevant *Side-effects* for most drugs are included in the monographs. However, if a class of drugs (e.g. tetracyclines, p. 277) share the same side-effects, these are presented in the prescribing notes while those unique to a particular drug in that class are included in its individual drug monograph. Occasionally, side-effects may be included within a preparation record if they are specific to that preparation or if the preparation is not accompanied by a monograph.

Side-effects are generally listed in order of frequency and arranged broadly by body systems. Occasionally a rare side-effect might be listed first if it is considered to be particularly important because of its seriousness. The frequency of side-effects is described in fig. 1.

An exhaustive list of side-effects is not included for drugs that are used by specialists (e.g. cytotoxic drugs and drugs used in anaesthesia). Recognising that hypersensitivity reactions can occur with virtually all medicines, this effect is generally not listed, unless the drug carries an increased risk of such reactions. BNFC also omits effects that are likely to have little clinical consequence (e.g. transient increase in liver enzymes).

The prescribing notes in BNFC may highlight important safety concerns and differences between drugs in their ability to cause certain side-effects. Safety warnings issued by the Commission on Human Medicines (CHM) or Medicines and Healthcare products Regulatory Agency (MHRA) can also be found here or in the drug monographs.

Adverse Reactions to Drugs (p. 11) provides advice on preventing adverse drug reactions, and guidance on reporting adverse drug reactions to the MHRA. The black triangle symbol ▼ identifies those preparations in BNFC that require additional monitoring by the European Medicines Agency.

Finding significant changes in BNFC

The print edition of BNFC is published in July each year, and monthly updates are provided online via bnf.org, *MedicinesComplete*, and the NHS Evidence portal. BNFC includes lists of changes that are relevant to clinical practice:

- *Changes* (p. xvii), provides a list of significant changes, dose changes, classification changes, new names, and new preparations that have been incorporated into BNFC, as well as a list of preparations that have been discontinued and removed from BNFC. For ease of identification, the margins of these pages are marked in pink. Changes listed online are cumulative (from one print edition to the next), and can be printed off each month to show the main changes since the last print edition as an aide memoire for those using print copies.
- *E-newsletter*, the BNF & BNFC e-newsletter service is available free of charge. It alerts healthcare professionals to details of significant changes in the clinical content of these publications and to

the way that this information is delivered. Newsletters also review clinical case studies and provide tips on using these publications effectively. To sign up for e-newsletters go to bnf.org/newsletter. To visit the e-newsletter archive, go to bnf.org/bnf/org_450066.htm.

So many changes are made for each update of BNFC, that not all of them can be accommodated in the *Changes* section. We encourage healthcare professionals to review regularly the prescribing information on drugs that they encounter frequently.

Nutrition

Appendix 2 (p. 771) includes tables of ACBS-approved enteral feeds and nutritional supplements based on their energy and protein content. There are separate tables for specialised formulae for specific clinical conditions. Classified sections on foods for special diets and nutritional supplements for metabolic diseases are also included.

Licensed status of medicines

BNFC includes advice on the use of unlicensed medicines or of licensed medicines for unlicensed applications ('off-label' use). Such advice reflects careful consideration of the options available to manage a given condition and the weight of evidence and experience of the unlicensed intervention. Limitations of the marketing authorisation should not preclude unlicensed use where clinically appropriate.

The *Licensed Use* statement in a drug monograph is used to indicate that:

- a drug is not licensed in the UK (e.g. potassium canrenoate, p. 80);
- a drug is licensed in the UK, but not for use in children (e.g. lansoprazole, p. 44);
- BNFC advice for certain indications, age groups of children, routes of administration, or preparations falls outside a drug's marketing authorisation (e.g. naproxen, p. 509).

The absence of the *Licensed Use* statement from a drug monograph indicates that the drug is licensed for all indications given in the monograph (e.g. zanamivir, p. 332).

Prescribing unlicensed medicines or medicines outside their marketing authorisation alters (and probably increases) the prescriber's professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines. Further information can be found in *BNF for Children* and Marketing Authorisation, p. 2.

Prices in BNFC

Basic NHS **net prices** are given in BNFC to provide an indication of relative cost. Where there is a choice of suitable preparations for a particular disease or condition the relative cost may be used in making a selection. Cost-effective prescribing must, however, take into account other factors (such as dose frequency and duration of treatment) that affect the total cost. The use of more expensive drugs is justified if it will result in better treatment of the patient, or a reduction of the length of an illness, or the time spent in hospital. We

regularly update prices using the Drug Tariff and proprietary price information published by the NHS dictionary of medicines and devices (dm+d, www.dmd.nhs.uk). The weekly updated dm+d data (including prices) can be accessed using the dm+d browser of the NHS Business Services Authority (www.ppa.org.uk/systems/pccdbrowserv2_3new/browser.jsp).

Prices have generally been calculated from the net cost used in pricing NHS prescriptions in April 2014 (for proprietary and non-proprietary preparations). Prices generally reflect whole dispensing packs; prices for injections are stated per ampoule, vial, or syringe. Prices for extemporaneously prepared preparations are not provided in BNFC as prices vary between different manufacturers.

BNFC prices are not suitable for quoting to patients seeking private prescriptions or contemplating over-the-counter purchases because they do not take into account VAT, professional fees, and other overheads.

A fuller explanation of costs to the NHS may be obtained from the Drug Tariff. Separate drug tariffs are applicable to England and Wales (www.ppa.org.uk/ppa/edt_intro.htm), Scotland (www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/), and Northern Ireland (www.dhsspsni.gov.uk/pas-tariff); prices in the different tariffs may vary.

Extra resources on the BNF website

While the BNF website (bnf.org) provides online access to BNFC content, it also provides additional resources such as an archive of the e-newsletter and policies.

Changes

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

Significant changes

Significant changes have been made in the following sections for *BNF for Children 2014–2015*:

The term ‘corrected gestational age’ replaces ‘post-menstrual age’ [How to use BNF for Children: Selecting the dose]

Interchangeability of oral mesalazine preparations, section 1.5.1

Haloperidol [significant changes to indications and doses], section 4.2.1

Metoclopramide: risk of neurological adverse effects—restricted indications, dose and duration of use [MHRA advice], section 4.6

Domperidone: risk of cardiac side-effects—restricted indication, new contra-indications, reduced dose and duration of use [MHRA advice], section 4.6

Codeine products: restricted use of codeine in children [MHRA/CHM advice], section 4.7.2

Antiepileptic drugs: new advice on switching between different manufacturers’ products for a particular drug [MHRA/CHM advice], section 4.8.1

Treatment of epilepsy [updated guidance], section 4.8.1

Clostridium difficile infection, section 5.1, Table 1

Prevention of secondary case of *Haemophilus influenzae* type b disease, section 5.1, Table 2

Prevention of pertussis [contacts requiring antibacterial prophylaxis], section 5.1, Table 2

Colistimethate sodium by dry powder inhalation for pseudomonal lung infection in cystic fibrosis [NICE guidance], section 5.1.7

Oral ketoconazole no longer recommended for treatment of fungal infections [CHMP advice], section 5.2.2

Malaria prophylaxis recommendations for specific countries, section 5.4.1

Mefloquine [risk of neuropsychiatric reactions], section 5.4.1

Driving guidance for patients with diabetes, BNF section 6.1

Liothyronine [monitoring required when switching to brands not licensed in the UK], section 6.2.1

Combined hormonal contraceptives [interactions with rifabutin and rifampicin], section 7.3.1

Risk of venous thromboembolism with combined hormonal contraceptives, section 7.3.1

Serious hypersensitivity reactions with intravenous iron [MHRA/CHM advice], section 9.1.1.2

Hydroxyethyl starch (HES) infusions [withdrawn as benefits no longer outweigh risks], section 9.2.2.2

Drugs unsafe for use in acute porphyrias, section 9.8.2

Diclofenac [updated contra-indications], section 10.1.1

Otitis externa and media [use of ototoxic ear drops in patients with perforated tympanic membrane or patent grommet updated], section 12.1.1 and section 12.1.2

Influenza vaccines [extension of childhood seasonal influenza vaccine programme], section 14.4

Meningococcal vaccines [changes to schedule for meningococcal group C conjugate vaccine], section 14.4

Rabies vaccine, section 14.4

Rotavirus vaccine [rotavirus vaccine introduced into childhood immunisation schedule], section 14.4

Local anaesthetic-induced cardiovascular toxicity [advice on management], section 15.2

Dose changes

Changes in dose statements introduced into *BNF for Children 2014–2015*:

Alfentanil, p. 645

Amoxicillin [oral dose], p. 265

Ampicillin [oral dose], p. 265

Arginine, p. 498

Aripiprazole [Treatment and recurrence prevention of mania], p. 177

Beriner[®] [short-term prophylaxis of hereditary angioedema before dental, medical, or surgical procedures], p. 161

Chloroquine [prophylaxis of malaria], p. 343

Clobazam [licensed age], p. 235

Co-codamol [restricted use of codeine in children], p. 201

Codeine [restricted use of codeine in children], p. 205

Domperidone, p. 196

Exocin[®] [not recommended for use in children under 1 year], p. 526

Fenofibrate [dose with concomitant statin], p. 129 and p. 129

Gentamicin [neonatal dose and monitoring], p. 281

Glypressin[®], p. 393

Granisetron, p. 197

Haloperidol, p. 174

Ipocol[®], p. 50

Iron sucrose, p. 451

Lacosamide [loading dose], p. 223

Malarone[®] Paediatric (proguanil hydrochloride with atovaquone) [prophylaxis of malaria], p. 346

Metronidazole [intravenous dose for neonates and children under 2 months], p. 299

Miconazole, p. 552

Migraleve[®] [licensed dose], p. 203

Naloxone [overdosage with opioids], p. 28

Ondansetron, p. 197

Paracetamol [oral and rectal doses in children aged under 3 months, intravenous doses, maximum doses in postoperative pain], p. 200

Pentasa[®], p. 50

Rifampicin [dose for prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive], p. 259

Rosuvastatin [dose with concomitant drugs], p. 126

Salofalk®, p. 51

Sodium benzoate, p. 499

Sodium phenylbutyrate, p. 499

Variquel®, p. 393

Classification changes

Classification changes have been made in the following sections of *BNF for Children 2014–2015*:

Section 5.4.1 Non-falciparum malaria (treatment) [title change]

Section 14.4 Trivalent seasonal influenza vaccines for intramuscular use [title change]

Section 14.4 Tetravalent seasonal influenza vaccine for intramuscular use [title change]

Section 14.4 Trivalent seasonal influenza vaccine for intranasal use [title change]

New names

Name changes introduced into *BNF for Children 2014–2015*:

HCU cooler® 15 [formerly *HCU cooler*®], p. 812

Levocarnitine [formerly carnitine], p. 494

MSUD cooler® 15 [formerly *MSUD cooler*®], p. 813

Pamidronate disodium [formerly Disodium pamidronate], p. 395

TYR cooler® 15 [formerly *TYR cooler*®], p. 818

Deleted preparations

Preparations listed below have been discontinued during the compilation of *BNF for Children 2014–2015*:

Amsacrine

Amsidine®

Anapen® preparations

Anexate®

Becodisks®

Broflex®

Cefpodoxime

Clonazepam injection

Diazoxide injection

Dibenyline®

Diprobath®

Dulcolax® *Pico Perles*

Duraphat® mouthwash

Ebetrex®

Epanutin® capsules [generic now available]

Eudemine® injection

Femulen®

Fenbid Spansules®

Fersamal®

Flunisolide

Forceval Junior® capsules

Fulsovin®

Furadantin®

Haldol® tablets [generic still available]

Half-Inderal LA®

Hydromol® *HC Intensive*

HyperHAES®

Inderal-LA®

Ketoconazole tablets

Liposic®

Hydrocortisone eye ointment

Meningitec®

Mesren®

Motilium® suppositories

Mouthwash solution-tablets [not considered suitable for inclusion by the Dental Advisory Group]

Mysoline® [generic now available]

Neo-Mercazole®

Nizoral® tablets

Novgos®

Orelox®

Otospurin®

Piperazine

Pitressin®

Pripsen®

Rivotril® injection

Sanomigran® elixir

Serevent diskhaler®

Stelazine® syrup

Syntaris®

Tetraspan®

Tevagrastim®

Thymol [mouthwash solution-tablets] [not considered suitable for inclusion by the Dental Advisory Group]

Topal®

Triiodothyronine

Valoid® tablets

Visclair®

Vividrin® nasal spray

Volulyte®

Voluven®

New preparations

New preparations included in the relevant sections of *BNF for Children 2014–2015*:

Amias® [candesartan cilexetil], p. 102

Artelac® *Nighttime Gel* [carbomer], p. 536

Artelac Rebalance® [sodium hyaluronate], p. 538

Bexsero® [meningococcal group B vaccine], p. 621

Colobreathe® [colistimethate sodium], p. 292

Ditropan® elixir [oxybutynin hydrochloride], p. 416

Dolocodon® *PR* [oxycodone], p. 211

Dropodex® [dexamethasone], p. 528

Emerade® [adrenaline], p. 160

Emustil® [soybean oil], p. 538

- Eurartesim*® [piperaquine with arteminol], p. 344
- Fluarix Tetra*® [influenza vaccine], p. 617
- Isentress*® chewable tablets [raltegravir], p. 325
- Kalydeco*® [ivacaftor], p. 165
- Liothyronine sodium injection, p. 373
- Liquivisc*® [carbomers], p. 536
- Longtec*® [oxycodone], p. 211
- LPL 63.4*® emollient bath additive, p. 561
- Lubristil Gel* [sodium hyaluronate, xanthan gum], p. 538
- Noyada*® [captopril], p. 100
- Octasa*® [mesalazine], p. 50
- Pegasys*® [peginterferon alfa], p. 445
- Pheburane*® [sodium phenylbutyrate], p. 500
- Phenytoin capsules [new generic], p. 228
- Primidone [new generic], p. 227
- Relvar Ellipta*® [fluticasone furoate with vilanterol], p. 149
- SAYANA PRESS*® [medroxyprogesterone acetate], p. 410
- Terra-Cortril*® [hydrocortisone with oxytetracycline], p. 567
- Tivicay*® [dolutegravir], p. 324
- Tranexamic acid injection, p. 122
- Ursofalk*® tablets [ursodeoxycholic acid], p. 68
- ViraferonPeg*® [peginterferon alfa], p. 446
- Xalatan*® [latanoprost], p. 533
- Zonegran*® [zonisamide], p. 234

General guidance

General guidance

Medicines should be given to children only when they are necessary, and in all cases the potential benefit of administering the medicine should be considered in relation to the risk involved. This is particularly important during pregnancy, when the risk to both mother and fetus must be considered (for further details see Prescribing in Pregnancy, p. 15).

It is important to discuss treatment options carefully with the child and the child's carer (see also Taking Medicines to Best Effect, below). In particular, the child and the child's carer should be helped to distinguish the adverse effects of prescribed drugs from the effects of the medical disorder. When the beneficial effects of the medicine are likely to be delayed, this should be highlighted.

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

- difficulty in taking the medicine (e.g. inability to swallow the medicine);
- unattractive formulation (e.g. unpleasant taste);
- prescription not collected or not dispensed;
- purpose of medicine not clear;
- perceived lack of efficacy;
- real or perceived adverse effects;
- carers' or child's perception of the risk and severity of side-effects may differ from that of the prescriber;
- instructions for administration not clear.

The prescriber, the child's carer, and the child (if appropriate) should agree on the health outcomes desired and on the strategy for achieving them ('concordance'). The prescriber should be sensitive to religious, cultural, and personal beliefs of the child's family that can affect acceptance of medicines.

Taking the time to explain to the child (and carers) the rationale and the potential adverse effects of treatment may improve adherence. Reinforcement and elaboration of the physician's instructions by the pharmacist and other members of the healthcare team can be important. Giving advice on the management of adverse effects and the possibility of alternative treatments may encourage carers and children to seek advice rather than merely abandon unacceptable treatment.

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

Drug treatment in children Children, and particularly neonates, differ from adults in their response to

drugs. Special care is needed in the neonatal period (first 28 days of life) and doses should always be calculated with care; the risk of toxicity is increased by a reduced rate of drug clearance and differing target organ sensitivity.

For guidance on selecting doses of drugs in children see *How to Use BNF for Children*, p. xiii.

Administration of medicines to children Children should be involved in decisions about taking medicines and encouraged to take responsibility for using them correctly. The degree of such involvement will depend on the child's age, understanding, and personal circumstances.

Occasionally a medicine or its taste has to be disguised or masked with small quantities of food. However, unless specifically permitted (e.g. some formulations of pancreatin), a medicine should **not** be mixed with large quantities of food because the full dose might not be taken and the child might develop an aversion to food if the medicine imparts an unpleasant taste. Medicines should **not** be mixed or administered in a baby's feeding bottle.

Children under 5 years (and some older children) find a liquid formulation more acceptable than tablets or capsules. However, for long-term treatment it may be possible for a child to be taught to take tablets or capsules.

An oral syringe (see below) should be used for accurate measurement and controlled administration of an oral liquid medicine. The unpleasant taste of an oral liquid can be disguised by flavouring it or by giving a favourite food or drink immediately afterwards, but the potential for food-drug interactions should be considered.

Advice should be given on dental hygiene to those receiving medicines containing cariogenic sugars for long-term treatment; sugar-free medicines should be provided whenever possible.

Children with nasal feeding tubes in place for prolonged periods should be encouraged to take medicines by mouth if possible; enteric feeding should generally be interrupted before the medicine is given (particularly if enteral feeds reduce the absorption of a particular drug). Oral liquids can be given through the tube provided that precautions are taken to guard against blockage; the dose should be washed down with warm water. When a medicine is given through a nasogastric tube to a neonate, **sterile water** must be used to accompany the medicine or to wash it down.

The intravenous route is generally chosen when a medicine cannot be given by mouth; reliable access, often a central vein, should be used for children whose treatment involves irritant or inotropic drugs or who need to receive the medicine over a long period or for home therapy. The subcutaneous route is used most commonly for insulin administration. Intramuscular

injections should preferably be **avoided** in children, particularly neonates, infants, and young children. However, the intramuscular route may be advantageous for administration of single doses of medicines when intravenous cannulation would be more problematic or painful to the child. Certain drugs, e.g. some vaccines, are only administered intramuscularly.

The intrathecal, epidural and intrasosseous routes should be used **only** by staff specially trained to administer medicines by these routes. Local protocols for the management of intrathecal injections must be in place (section 8.1).

Managing medicines in school Administration of a medicine during schooltime should be avoided if possible; medicines should be prescribed for once or twice-daily administration whenever practicable. If the medicine needs to be taken in school, this should be discussed with parents or carers and the necessary arrangements made in advance; where appropriate, involvement of a school nurse should be sought. *Managing Medicines in Schools and Early Years Settings* produced by the Department of Health provides guidance on using medicines in schools (www.dh.gov.uk).

Patient information leaflets Manufacturers' patient information leaflets that accompany a medicine, cover only the licensed use of the medicine (see *BNF for Children* and Marketing Authorisation, below). Therefore, when a medicine is used outside its licence, it may be appropriate to advise the child and the child's parent or carer that some of the information in the leaflet might not apply to the child's treatment. Where necessary, inappropriate advice in the patient information leaflet should be identified and reassurance provided about the correct use in the context of the child's condition.

Biosimilar medicines A biosimilar medicine is a new biological product that is similar to a medicine that has already been authorised to be marketed (the biological reference medicine) in the European Union. The active substance of a biosimilar medicine is similar, but not identical, to the biological reference medicine. Biological products are different from standard chemical products in terms of their complexity and although theoretically there should be no important differences between the biosimilar and biological reference medicine in terms of safety or efficacy, when prescribing biological products, it is good practice to use the brand name. This will ensure that substitution of a biosimilar medicine does not occur when the medicine is dispensed.

Biosimilar medicines have black triangle status (▼, see p. 12) at the time of initial marketing. It is important to report suspected adverse reactions to biosimilar medicines using the Yellow Card Scheme (p. 11). For biosimilar medicines, adverse reaction reports should clearly state the brand name and the batch number of the suspected medicine.

Complementary and alternative medicine An increasing amount of information on complementary and alternative medicine is becoming available. Where appropriate, the child and the child's carers should be asked about the use of their medicines, including dietary supplements and topical products. The scope of *BNF for Children* is restricted to the discussion of conventional medicines but reference is made to complementary treatments if they affect conventional therapy (e.g. interactions with St John's wort—see Appendix 1).

Further information on herbal medicines is available at www.mhra.gov.uk.

BNF for Children and marketing authorisation

Where appropriate the *doses, indications, cautions, contra-indications, and side-effects* in *BNF for Children* reflect those in the manufacturers' Summaries of Product Characteristics (SPCs) which, in turn, reflect those in the corresponding marketing authorisations (formerly known as Product Licences). *BNF for Children* does not generally include proprietary medicines that are not supported by a valid Summary of Product Characteristics or when the marketing authorisation holder has not been able to supply essential information. When a preparation is available from more than one manufacturer, *BNF for Children* reflects advice that is the most clinically relevant regardless of any variation in the marketing authorisation. Unlicensed products can be obtained from 'special-order' manufacturers or specialist importing companies, see p. 840.

As far as possible, medicines should be prescribed within the terms of the marketing authorisation. However, many children require medicines not specifically licensed for paediatric use. Although medicines cannot be promoted outside the limits of the licence, the Human Medicines Regulations 2012 do not prohibit the use of unlicensed medicines.

BNF for Children includes advice involving the use of unlicensed medicines or of licensed medicines for unlicensed uses ('off-label' use). Such advice reflects careful consideration of the options available to manage a given condition and the weight of evidence and experience of the unlicensed intervention (see also Unlicensed Medicines, p. 6). Where the advice falls outside a drug's marketing authorisation, *BNF for Children* shows the licensing status in the drug monograph. However, limitations of the marketing authorisation should not preclude unlicensed use where clinically appropriate.

Prescribing unlicensed medicines

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

Drugs and skilled tasks Prescribers and other healthcare professionals should advise children and their carers if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient's fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

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

Excipients Branded oral liquid preparations that do not contain *fructose, glucose, or sucrose* are described as

'sugar-free' in *BNF for Children*. Preparations containing hydrogenated glucose syrup, mannitol, maltitol, sorbitol, or xylitol are also marked 'sugar-free' since they do not cause dental caries. Children receiving medicines containing cariogenic sugars, or their carers, should be advised of dental hygiene measures to prevent caries. Sugar-free preparations should be used whenever possible, particularly if treatment is required for a long period.

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

Information is provided on *selected excipients* in skin preparations (section 13.1.3), in vaccines (section 14.1), and on *selected preservatives and excipients* in eye drops and injections.

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

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

The *lactose* content in most medicines is too small to cause problems in most lactose-intolerant children. However in severe lactose intolerance, the lactose content should be determined before prescribing. The amount of lactose varies according to manufacturer, product, formulation, and strength.

Important

In the absence of information on excipients in *BNF for Children* and in the product literature (available at www.medicines.org.uk/emc/), contact the manufacturer (see Index of Manufacturers) if it is essential to check details.

Health and safety When handling chemical or biological materials particular attention should be given to the possibility of allergy, fire, explosion, radiation, or poisoning. Care is required to avoid sources of heat (including hair dryers) when flammable substances are used on the skin or hair. Substances, such as corticosteroids, some antimicrobials, phenothiazines, and many cytotoxics, are irritant or very potent and should be handled with caution; contact with the skin and inhalation of dust should be avoided. Healthcare professionals and carers should guard against exposure to sensitising, toxic or irritant substances if it is necessary to crush tablets or open capsules.

EEA and Swiss prescriptions Pharmacists can dispense prescriptions issued by doctors and dentists from the European Economic Area (EEA) or Switzerland (except prescriptions for controlled drugs in Schedules 1, 2, or 3, or for drugs without a UK marketing authorisation). Prescriptions should be written in ink or otherwise so as to be indelible, should be dated, should state the name of the patient, should state the address of the

prescriber, should contain particulars indicating whether the prescriber is a doctor or dentist, and should be signed by the prescriber.

Security and validity of prescriptions The Councils of the British Medical Association and the Royal Pharmaceutical Society have issued a joint statement on the security and validity of prescriptions.

In particular, prescription forms should:

- not be left unattended at reception desks;
- not be left in a car where they may be visible; and
- when not in use, be kept in a locked drawer within the surgery and at home.

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

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

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

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

Prescription writing

Shared care

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

Prescriptions¹ should be written legibly in ink or otherwise so as to be indelible², should be dated, should state the full name and address of the patient, the address of the prescriber, an indication of the type of prescriber, and should be signed in ink by the prescriber³. The age and the date of birth of the child should preferably be stated, and it is a legal requirement in the case of prescription-only medicines to state the age for children under 12 years.

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

The following should be noted:

- The strength or quantity to be contained in capsules, lozenges, tablets, etc. should be stated by the prescriber. In particular, strengths of liquid preparations should be clearly stated (e.g. 125 mg/5 mL).
- The unnecessary use of decimal points should be avoided, e.g. 3 mg, not 3.0 mg.
Quantities of 1 gram or more should be written as 1 g, etc.
Quantities less than 1 gram should be written in milligrams, e.g. 500 mg, not 0.5 g.
Quantities less than 1 mg should be written in micrograms, e.g. 100 micrograms, not 0.1 mg.
When decimals are unavoidable a zero should be written in front of the decimal point where there is no other figure, e.g. 0.5 mL, not .5 mL.
Use of the decimal point is acceptable to express a range, e.g. 0.5 to 1 g.
- 'Micrograms' and 'nanograms' should **not** be abbreviated. Similarly 'units' should **not** be abbreviated.
- The term 'millilitre' (mL or mL)⁴ is used in medicine and pharmacy, and cubic centimetre, c.c., or cm³ should not be used.
- Dose and dose frequency should be stated; in the case of preparations to be taken 'as required' a **minimum dose interval** should be specified.
Care should be taken to ensure the child receives the correct dose of the active drug. Therefore, the dose should normally be stated in terms of the mass of the active drug (e.g. '125 mg 3 times daily'); terms

such as '5 mL' or '1 tablet' should be avoided except for compound preparations.

When doses other than multiples of 5 mL are prescribed for *oral liquid preparations* the dose-volume will be provided by means of an **oral syringe**, see p. 2 (except for preparations intended to be measured with a pipette).

- For suitable quantities of dermatological preparations, see section 13.1.2.
- The names of drugs and preparations should be written clearly and **not** abbreviated, using approved titles **only** (see also advice in box on p. 5 to **avoid** creating generic titles for modified-release preparations).
- The quantity to be supplied may be stated by indicating the number of days of treatment required in the box provided on NHS forms. In most cases the exact amount will be supplied. This does not apply to items directed to be used as required—if the dose and frequency are not given then the quantity to be supplied needs to be stated.
When several items are ordered on one form the box can be marked with the number of days of treatment provided the quantity is added for any item for which the amount cannot be calculated.
- Although directions should preferably be in **English without abbreviation**, it is recognised that some Latin abbreviations are used (for details see Inside Back Cover).

For a sample prescription, see below.

Pharmacy Stamp	Age 1yr 3mths	Title, Forename, Surname & Address Master Peter Patient
	D.o.B. 2/4/2010	Flat 1 50 Stanhope Street Newtown TE22 1ST
Please don't stamp over age box		
Number of days' treatment N.B. Ensure dose is stated	5	
Endorsements Amoxicillin oral suspension 125mg/5mL sugar-free 125mg three times daily Supply 100mL [No more items on this prescription]		
Signature of prescriber <i>Dr D O Good</i>		Date 02/07/11
For dispenser No. of Prescs. on form	Anyborough Health Authority Dr D O Good 345543 7 High Street Anytown KB1 CD2 Tel: 0111 222 333	
NHS		FP10NC0105

- These recommendations are acceptable for **prescription-only medicines** (POM). For items marked (C2), (C3), (C4+1), and (C4+2), see also Prescribing Controlled Drugs, p. 8.
- It is permissible to issue carbon copies of NHS prescriptions as long as they are signed in ink.
- Computer-generated facsimile signatures do not meet the legal requirement.
- The use of capital 'L' in mL is a printing convention throughout *BNF for Children*; both 'mL' and 'ml' are recognised SI abbreviations.

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

Non-proprietary titles Where non-proprietary ('generic') titles are given, they should be used for prescribing. This will enable any suitable product to be dispensed, thereby saving delay to the patient and sometimes expense to the health service. The only exception is where there is a demonstrable difference in clinical effect between each manufacturer's version of the formulation, making it important that the child should always receive the same brand; in such cases, the brand name or the manufacturer should be stated.

Non-proprietary names of compound preparations

Non-proprietary names of **compound preparations** which appear in *BNF for Children* are those that have been compiled by the British Pharmacopoeia Commission or another recognised body; whenever possible they reflect the names of the active ingredients. Prescribers should avoid creating their own compound names for the purposes of generic prescribing; such names do not have an approved definition and can be misinterpreted.

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

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

Supply of medicines

When supplying a medicine for a child, the pharmacist should ensure that the child and the child's carer understand the nature and identity of the medicine and how it should be used. The child and the carer should be provided with appropriate information (e.g. how long the medicine should be taken for and what to do if a dose is missed or the child vomits soon after the dose is given).

Safety in the home Carers and relatives of children must be warned to keep all medicines out of the reach and sight of children. Tablets, capsules and oral and external liquid preparations must be dispensed in a reclosable *child-resistant container* unless:

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

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

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

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

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

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

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

Unlicensed medicines A drug or formulation that is not covered by a marketing authorisation (see also *BNF for Children* and Marketing Authorisation) may be obtained from a pharmaceutical company, imported by a specialist importer, manufactured by a commercial or hospital licensed manufacturing unit (see *Special-order Manufacturers*, p. 840), or prepared extemporaneously (see below) against a prescription.

The safeguards that apply to products with marketing authorisation should be extended, as far as possible, to the use of unlicensed medicines. The safety, efficacy, and quality (including labelling) of unlicensed medicines should be assured by means of clear policies on their prescribing, purchase, supply, and administration. Extra

care is required with unlicensed medicines because less information may be available on the drug and any formulation of the drug.

The following should be agreed with the supplier when ordering an unlicensed or extemporaneously prepared medicine:

- the specification of the formulation;
- documentation confirming the specification and quality of the product supplied (e.g. a certificate of conformity or of analysis);
- for imported preparations product and licensing information should be supplied in English.

Extemporaneous preparations A product should be dispensed extemporaneously only when no product with a marketing authorisation is available. Every effort should be made to ensure that an extemporaneously prepared product is stable and that it delivers the requisite dose reliably; the child should be provided with a consistent formulation regardless of where the medicine is supplied to minimise variations in quality. Where there is doubt about the formulation, advice should be sought from a medicines information centre, the pharmacy at a children's hospital, a hospital production unit, a hospital quality control department, or the manufacturer.

In many cases it is preferable to give a licensed product by an unlicensed route (e.g. an injection solution given by mouth) than to prepare a special formulation. When tablets or capsules are cut, dispersed, or used for preparing liquids immediately before administration, it is important to confirm uniform dispersal of the active ingredient, especially if only a portion of the solid content (e.g. a tablet segment) is used or if only an aliquot of the liquid is to be administered.

In some cases the child's clinical condition may require a dose to be administered in the absence of full information on the method of administration. It is important to ensure that the appropriate supporting information is available at the earliest opportunity.

Preparation of products that produce harmful dust (e.g. cytotoxic drugs, hormones, or potentially sensitising drugs such as neomycin) should be **avoided** or undertaken with appropriate precautions to protect staff and carers (see also *Safety in the Home*, above).

The BP direction that a preparation must be *freshly prepared* indicates that it must be made not more than 24 hours before it is issued for use. The direction that a preparation should be *recently prepared* indicates that deterioration is likely if the preparation is stored for longer than about 4 weeks at 15–25°C.

The term **water** used without qualification means either potable water freshly drawn direct from the public supply and suitable for drinking or freshly boiled and cooled purified water. The latter should be used if the public supply is from a local storage tank or if the potable water is unsuitable for a particular preparation. See also *Water for Injections*, section 9.2.2.

Emergency supply of medicines

Emergency supply requested by member of the public

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

- (a) that the pharmacist has interviewed the person requesting the prescription-only medicine and is satisfied:
 - (i) that there is immediate need for the prescription-only medicine and that it is impracticable in the circumstances to obtain a prescription without undue delay;
 - (ii) that treatment with the prescription-only medicine has on a previous occasion been prescribed for the person requesting it;
 - (iii) as to the dose that it would be appropriate for the person to take;
- (b) that no greater quantity shall be supplied than will provide 5 days' treatment of phenobarbital, phenobarbital sodium, or Controlled Drugs in Schedules 4 or 5,¹ or 30 days' treatment for other prescription-only medicines, except when the prescription-only medicine is:
 - (i) insulin, an ointment or cream, or a preparation for the relief of asthma in an aerosol dispenser when the smallest pack can be supplied;
 - (ii) an oral contraceptive when a full cycle may be supplied;
 - (iii) an antibiotic in liquid form for oral administration when the smallest quantity that will provide a full course of treatment can be supplied;
- (c) that an entry shall be made by the pharmacist in the prescription book stating:
 - (i) the date of supply;
 - (ii) the name, quantity, and, where appropriate, the pharmaceutical form and strength;
 - (iii) the name and address of the patient;
 - (iv) the nature of the emergency;
- (d) that the container or package must be labelled to show:
 - (i) the date of supply;
 - (ii) the name, quantity, and, where appropriate, the pharmaceutical form and strength;
 - (iii) the name of the patient;
 - (iv) the name and address of the pharmacy;
 - (v) the words 'Emergency supply';
 - (vi) the words 'Keep out of the reach of children' (or similar warning);

- (e) that the prescription-only medicine is not a substance specifically excluded from the emergency supply provision, and does not contain a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital or phenobarbital sodium for the treatment of epilepsy: for details see *Medicines, Ethics and Practice*, London, Pharmaceutical Press (always consult latest edition).¹

Emergency supply requested by prescriber

Emergency supply of a prescription-only medicine may also be made at the request of a doctor, a dentist, a supplementary prescriber, a community practitioner nurse prescriber, a nurse, pharmacist or optometrist independent prescriber, or a doctor or dentist from the European Economic Area or Switzerland, provided:

- (a) that the pharmacist is satisfied that the prescriber by reason of some emergency is unable to furnish a prescription immediately;
- (b) that the prescriber has undertaken to furnish a prescription within 72 hours;
- (c) that the medicine is supplied in accordance with the directions of the prescriber requesting it;
- (d) that the medicine is not a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital or phenobarbital sodium for the treatment of epilepsy: for details see *Medicines, Ethics and Practice*, London, Pharmaceutical Press (always consult latest edition).¹
- (e) that an entry shall be made in the prescription book stating:
 - (i) the date of supply;
 - (ii) the name, quantity, and, where appropriate, the pharmaceutical form and strength;
 - (iii) the name and address of the practitioner requesting the emergency supply;
 - (iv) the name and address of the patient;
 - (v) the date on the prescription;
 - (vi) when the prescription is received the entry should be amended to include the date on which it is received.

Royal Pharmaceutical Society's guidelines

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

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

1. Doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs in schedules 1, 2, or 3, or drugs that do not have a UK marketing authorisation.

Prescribing Controlled Drugs

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

Class A includes: alfentanil, cocaine, diamorphine (heroin), dipipanone, lysergide (LSD), methadone, methylenedioxymethamphetamine (MDMA, 'ecstasy'), morphine, opium, pethidine, phencyclidine, remifentanyl, and class B substances when prepared for injection

Class B includes: oral amfetamines, barbiturates, cannabis, cannabis resin, codeine, ethylmorphine, glutethimide, nabilone, pentazocine, phenmetrazine, and pholcodine

Class C includes: certain drugs related to the amfetamines such as benzphetamine and chlorphentermine, buprenorphine, diethylpropion, mazindol, meprobamate, pemoline, pipradrol, most benzodiazepines, zolpidem, androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin

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

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

Schedule 2 includes drugs such as diamorphine (heroin), morphine, nabilone, remifentanyl, pethidine, secobarbital, glutethimide, alfentanil, and cocaine and are subject to the full controlled drug requirements relating to prescriptions, safe custody (except for secobarbital), the need to keep registers, etc. (unless exempted in Schedule 5).

Schedule 3 includes the barbiturates (except secobarbital, now Schedule 2), buprenorphine, diethylpropion, mazindol, meprobamate, midazolam, pentazocine, phentermine, and temazepam. They are subject to the special prescription requirements (except for temazepam) and to the safe custody requirements (except for any 5,5 disubstituted barbituric acid (e.g. phenobarbital), mazindol, meprobamate, midazolam, pentazocine, phentermine, or any stereoisomeric form or salts of the above). Records in registers do not need to be kept (although there are requirements for the retention of invoices for 2 years).

Schedule 4 includes in Part I benzodiazepines (except temazepam and midazolam which are in Schedule 3) and zolpidem, which are subject to minimal control. Part II includes androgenic and

anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin. Controlled Drug prescription requirements do not apply (but see Department of Health Guidance, p. 9) and Schedule 4 Controlled Drugs are not subject to safe custody requirements.

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

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

- **[CD2]** for preparations in Schedule 2;
- **[CD3]** for preparations in Schedule 3;
- **[CD4-1]** for preparations in Schedule 4 (Part I);
- **[CD4-2]** for preparations in Schedule 4 (Part II).

The principal legal requirements relating to medical prescriptions are listed below (see also Department of Health Guidance, p. 9).

Prescription requirements

Prescriptions for Controlled Drugs that are subject to prescription requirements¹ must be indelible² and must be *signed* by the prescriber, *be dated*, and specify the prescriber's *address*. The prescription must always state:

- The name and address of the patient;
- In the case of a preparation, the form³ and where appropriate the strength⁴ of the preparation;
- for liquids, the total volume in millilitres (in both words and figures) of the preparation to be supplied; for dosage units, the number (in both words and figures) of dosage units to be supplied; in any other case, the total quantity (in both words and figures) of the Controlled Drug to be supplied;
- The dose;⁵
- The words 'for dental treatment only' if issued by a dentist.

A pharmacist is **not** allowed to dispense a Controlled Drug unless all the information required by law is given on the prescription. In the case of a prescription for a Controlled Drug in Schedule 2 or 3, a pharmacist can amend the prescription if it specifies the total quantity only in words or in figures or if it contains minor typographical errors, provided that such amendments are indelible and clearly attributable to the pharmacist.⁶

1. All preparations in Schedules 2 and 3, except temazepam.
2. A machine-written prescription is acceptable. The prescriber's signature must be handwritten.
3. The dosage form (e.g. tablets) must be included on a Controlled Drugs prescription irrespective of whether it is implicit in the proprietary name (e.g. *MST Continus*) or whether only one form is available.
4. When more than one strength of a preparation exists the strength required must be specified.
5. The instruction 'one as directed' constitutes a dose but 'as directed' does not.
6. Implementation date for *N. Ireland* not confirmed.

Failure to comply with the regulations concerning the writing of prescriptions will result in inconvenience to patients and carers and delay in supply of the necessary medicine. A prescription for a Controlled Drug in Schedules 2, 3, or 4 is valid for 28 days from the date stated thereon.¹

Instalments and 'repeats' A prescription may order a Controlled Drug to be dispensed by instalments; the amount of instalments and the intervals to be observed must be specified.²

Instalment prescriptions must be dispensed in accordance with the directions in the prescription. However, the Home Office has approved specific wording which may be included in an instalment prescription to cover certain situations; for example, if a pharmacy is closed on the day when an instalment is due. For details see *Medicines, Ethics and Practice*, London, Pharmaceutical Press (always consult latest edition) or see *Drug Misuse and Dependence: UK Guidelines on Clinical Management* (2007), available at www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf.

Prescriptions ordering 'repeats' on the same form are not permitted for Controlled Drugs in Schedules 2 or 3.

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

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

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

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

For a sample prescription, see below.

Pharmacy Stamp		Age 1yr 3mths	Title, Forename, Surname & Address Master Peter Patient
Dose 2/4/2010		Flat 1 50 Stanhope Street Newtown TE22 1ST	
Please don't stamp over age box Number of days' treatment N.B. Ensure dose is stated			
Endorsements		Diamorphine 10mg injection 6mg daily by subcutaneous infusion over 24 hours Supply 6(six) ampoules [No more items on this prescription]	
Signature 		Date 02/07/11	
For dispenser No. of Prescrip. on form		Anyborough Health Authority Dr D O Good 345543 7 High Street Anytown KB1 CD2 Tel: 0111 222 333	
NHS		FP10NC0105	

Dependence and misuse The most serious drugs of addiction are **cocaine**, **diamorphine** (heroin), **morphine**, and the **synthetic opioids**.

Despite marked reduction in the prescribing of **amfetamines** there is concern that abuse of illicit amphetamine and related compounds is widespread.

Benzodiazepines are commonly misused. However, the misuse of **barbiturates** is now uncommon because of their declining medicinal use and consequent availability.

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

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

Prescribing drugs likely to cause dependence or misuse The prescriber has three main responsibilities:

- to avoid creating dependence by introducing drugs to patients without sufficient reason. In this context, the proper use of the morphine-like drugs is well understood. The dangers of other Controlled Drugs are less clear because recognition of dependence is not easy and its effects, and those of withdrawal, are less obvious;
- to see that the patient does not gradually increase the dose of a drug, given for good medical reasons, to the point where dependence becomes more

1. The prescriber may forward-date the prescription; the start date may also be specified in the body of the prescription.
2. A total of 14 days' treatment by instalment of any drug listed in Schedule 2 of the Misuse of Drugs Regulations, buprenorphine and diazepam may be prescribed in England. In *England*, forms FP10(MDA) (blue) and FP10H (MDA) (blue) should be used. In *Scotland*, forms GP10 (peach), HBP (blue), or HBPA (pink) should be used. In *Wales* a total of 14 days' treatment by instalment of any drug listed in Schedules 2–5 of the Misuse of Drugs Regulations may be prescribed. In *Wales*, form WP10(MDA) or form WP10HP(AD) should be used.

likely. The prescriber should keep a close eye on the amount prescribed to prevent patients or their carers from accumulating stocks. A minimal amount should be prescribed in the first instance, or when seeing a new patient for the first time;

- to avoid being used as an unwitting source of supply for addicts and being vigilant to methods for obtaining medicines which include visiting more than one doctor, fabricating stories, and forging prescriptions.

Patients under temporary care should be given only small supplies of drugs unless they present an unequivocal letter from their own doctor. It is sensible to reduce dosages steadily or to issue weekly or even daily prescriptions for small amounts if dependence is suspected.

The stealing and misuse of prescription forms could be minimised by the following precautions:

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

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

Applications must be supported by a covering letter from the prescriber and should give details of:

- the patient's name and current address;
- the quantities of drugs to be carried;
- the strength and form in which the drugs will be dispensed;
- the country or countries of destination;
- the dates of travel to and from the United Kingdom.

Applications for licences should be sent to the Home Office, Drugs Licensing, Peel Building, 2 Marsham Street, London, SW1P 4DF. Alternatively, completed application forms can be emailed to licensing_enquiry.aadu@homeoffice.gsi.gov.uk with a scanned copy of the covering letter from the prescriber. A minimum of two weeks should be allowed for processing the application.

Patients travelling for less than 3 months do not require a personal export/import licence for carrying Controlled Drugs, but are advised to carry a letter from the prescribing doctor. Those travelling for more than 3 months are advised to make arrangements to have their medication prescribed by a practitioner in the country they are visiting.

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

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

Notification of drug misusers

Doctors should report cases of drug misuse to their regional or national drug misuse database or centre—for further advice and contact telephone numbers consult the BNFC.

Adverse reactions to drugs

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

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

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

The reporting of **all** suspected adverse drug reactions, no matter how minor, in children under 18 years, including those relating to unlicensed or off-label use of medicines, is **strongly encouraged** through the Yellow Card Scheme even if the additional monitoring symbol (▼, see below) has been removed. This is because experience in children may still be limited.

The identification and reporting of adverse reactions to drugs in children is particularly important because:

- the action of the drug and its pharmacokinetics in children (especially in the very young) may be different from that in adults;
- drugs may not be extensively tested in children;
- children may be more susceptible to developmental disorders or they may have delayed adverse reactions which do not occur in adults;
- many drugs are not specifically licensed for use in children and are used 'off-label';
- suitable formulations may not be available to allow precise dosing in children;
- the nature and course of illnesses and adverse drug reactions may differ between adults and children.

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

A 24-hour Freephone service is available to all parts of the UK for advice and information on suspected adverse drug reactions; contact the National Yellow Card Information Service at the MHRA on 0800 731 6789. Outside

office hours a telephone-answering machine will take messages.

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

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

Yellow Card Centre Northern & Yorkshire
Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH
Tel: (0191) 260 6182

Yellow Card Centre Wales
Cardiff University
Department of Pharmacology, Therapeutics and Toxicology
Heath Park
Cardiff
CF14 4XN
Tel: (029) 2074 4181

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

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

The MHRA's database facilitates the monitoring of adverse drug reactions.

More detailed information on reporting and a list of products currently under additional monitoring can be found on the MHRA website:

www.mhra.gov.uk

MHRA Drug Safety Update

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

Self-reporting Patients and their carers can also report suspected adverse drug reactions to the MHRA. Reports can be submitted directly to the MHRA through the Yellow Card Scheme using the electronic form at yellowcard.mhra.gov.uk or by telephone on 0800 100 3352. Alternatively, patient Yellow Cards are available from pharmacies and GP surgeries, or can be downloaded from www.mhra.gov.uk, where more detailed information on patient reporting is available. Information for patients about the Yellow Card Scheme is available in other languages at yellowcard.mhra.gov.uk.

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

Newer drugs and vaccines Only limited information is available from clinical trials on the safety of new medicines. Further understanding about the safety of medicines depends on the availability of information from routine clinical practice.

The black triangle symbol (▼) identifies newly licensed medicines that require additional monitoring by the European Medicines Agency. Such medicines include new active substances, biosimilar medicines, and medicines that the European Medicines Agency consider require additional monitoring. The black triangle symbol also appears in the Patient Information Leaflets for relevant medicines, with a brief explanation of what it means. Products usually retain a black triangle for 5 years, but this can be extended if required.

Adverse reactions to medical devices Suspected adverse reactions to medical devices including dental or surgical materials, intra-uterine devices, and contact lens fluids should be reported. Information on reporting these can be found at:

www.mhra.gov.uk.

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

In the product literature the frequency of side-effects is generally described as follows:

Very common	greater than 1 in 10
Common	1 in 100 to 1 in 10
Uncommon ['less commonly' in <i>BNF for Children</i>]	1 in 1000 to 1 in 100
Rare	1 in 10 000 to 1 in 1000
Very rare	less than 1 in 10 000

Special problems

Symptoms Children may be poor at expressing the symptoms of an adverse drug reaction and parental opinion may be required.

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

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

Prevention of adverse reactions

Adverse reactions may be prevented as follows:

- never use any drug unless there is a good indication. If the patient is pregnant do not use a drug unless the need for it is imperative;
- allergy and idiosyncrasy are important causes of adverse drug reactions. Ask if the child has had previous reactions to the drug or formulation;
- prescribe as few drugs as possible and give very clear instructions to the child, parent, or carer;
- whenever possible use a familiar drug; with a new drug be particularly alert for adverse reactions or unexpected events;
- consider if excipients (e.g. colouring agents) may be contributing to the adverse reaction. If the reaction is minor, a trial of an alternative formulation of the same drug may be considered before abandoning the drug;
- obtain a full drug history including asking if the child is already taking other drugs *including over-the-counter medicines*; interactions may occur;
- age and hepatic or renal disease may alter the metabolism or excretion of drugs, particularly in neonates, which can affect the potential for adverse effects. Genetic factors may also be responsible for variations in metabolism, and therefore for the adverse effects of the drug;
- warn the child, parent, or carer if serious adverse reactions are liable to occur.

Defective medicines

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

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

The Defective Medicines Report Centre
Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road
London, SW1W 9SZ
Tel: (020) 3080 6588
info@mhra.gsi.gov.uk

Prescribing in hepatic impairment

Children have a large reserve of hepatic metabolic capacity and modification of the choice and dosage of drugs is usually unnecessary even in apparently severe liver disease. However, special consideration is required in the following situations:

- liver failure characterised by severe derangement of liver enzymes and profound jaundice; the use of sedative drugs, opioids, and drugs such as diuretics and amphotericin which produce hypokalaemia may precipitate hepatic encephalopathy;
- impaired coagulation, which can affect response to oral anticoagulants;
- in cholestatic jaundice elimination may be impaired of drugs such as fusidic acid and rifampicin which are excreted in the bile;

- in hypoproteinaemia, the effect of highly protein-bound drugs such as phenytoin, prednisolone, warfarin, and benzodiazepines may be increased;
- use of hepatotoxic drugs is more likely to cause toxicity in children with liver disease; such drugs should be avoided if possible;
- in neonates, particularly preterm neonates, and also in infants metabolic pathways may differ from older children and adults because liver enzyme pathways may be immature.

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

Prescribing in renal impairment

The use of drugs in children with reduced renal function can give rise to problems for several reasons:

- reduced renal excretion of a drug or its metabolites may produce toxicity;
- sensitivity to some drugs is increased even if elimination is unimpaired;
- many side-effects are tolerated poorly by children with renal impairment;
- some drugs are not effective when renal function is reduced;
- neonates, particularly preterm, may have immature renal function.

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

Principles of dose adjustment in renal impairment

The level of renal function below which the dose of a drug must be reduced depends on the proportion of the drug eliminated by renal excretion and its toxicity.

For many drugs with only minor or no dose-related side-effects, very precise modification of the dose regimen is unnecessary and a simple scheme for dose reduction is sufficient

For more toxic drugs with a small safety margin dose regimens based on glomerular filtration rate should be used. When both efficacy and toxicity are closely related to plasma-drug concentration, recommended regimens should be regarded only as a guide to initial treatment; subsequent doses must be adjusted according to clinical response and plasma-drug concentration.

The total daily maintenance dose of a drug can be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, although the size of the maintenance dose is reduced it is important to give a loading dose if an immediate effect is required. This is because it takes

about five times the half-life of the drug to achieve steady-state plasma concentration. Because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment, it can take many doses at the reduced dosage to achieve a therapeutic plasma concentration. The loading dose should usually be the same as the initial dose for a child with normal renal function.

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

Glomerular filtration rate is low at birth and increases rapidly during the first 6 months. Thereafter, glomerular filtration rate increases gradually to reach adult levels by 1–2 years of age, when standardised to a typical adult body surface area (1.73 m^2). In the first weeks after birth, serum creatinine falls; a single measure of serum creatinine provides only a crude estimate of renal function and observing the change over days is of more use. In the neonate, a sustained rise in serum creatinine or a lack of the expected postnatal decline, is indicative of a reduced glomerular filtration rate.

Dose recommendations are based on the severity of renal impairment. This is expressed in terms of **glomerular filtration rate** ($\text{mL/minute}/1.73 \text{ m}^2$).

The following equations provide a guide to glomerular filtration rate.

Child over 1 year:

Estimated glomerular filtration rate ($\text{mL/minute}/1.73 \text{ m}^2$) = $40^1 \times \text{height (cm)}/\text{serum creatinine (micromol/litre)}$

Neonate:

Estimated glomerular filtration rate ($\text{mL/minute}/1.73 \text{ m}^2$) = $30^1 \times \text{height (cm)}/\text{serum creatinine (micromol/litre)}$

1. The values used in these formulas may differ according to locality or laboratory.

The serum-creatinine concentration is sometimes used as a measure of renal function but is only a **rough guide** even when corrected for age, weight, and sex.

Important

The information on dose adjustment in *BNF for Children* is expressed in terms of estimated glomerular filtration rate.

Renal function in adults is increasingly being reported as estimated glomerular filtration rate (eGFR) normalised to a body surface area of 1.73 m^2 ; however, eGFR is derived from the MDRD (Modification of Diet in Renal Disease) formula which is not validated for use in children. eGFR derived from the MDRD formula should **not** be used to adjust drug doses in children with renal impairment.

In *BNF for Children*, values for measures of renal function are included where possible. However, where such values are not available, the *BNF for Children* reflects the terms used in the published information.

Chronic kidney disease in adults: UK guidelines for identification, management and referral (March 2006) defines renal function as follows:

Degree of impairment	eGFR ¹ mL/minute/ 1.73 m^2
Normal: Stage 1	More than 90 (with other evidence of kidney damage)
Mild: Stage 2	60–89 (with other evidence of kidney damage)
Moderate ² : Stage 3	30–59
Severe: Stage 4	15–29
Established renal failure: Stage 5	Less than 15
1. Estimated glomerular filtration rate (eGFR) derived from the Modification of Diet in Renal Disease (MDRD) formula for use in patients over 18 years 2. NICE clinical guideline 73 (September 2008)—Chronic kidney disease: Stage 3A eGFR = 45–59, Stage 3B eGFR = 30–44	

Dialysis

For prescribing in children on renal replacement therapy consult specialist literature.

Drug prescribing should be kept to the minimum in all children with severe renal disease.

If even mild renal impairment is considered likely on clinical grounds, renal function should be checked before prescribing **any** drug which requires dose modification.

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

Prescribing in pregnancy

Drugs can have harmful effects on the fetus at any time during pregnancy. It is important to bear this in mind when prescribing for a female of *childbearing age* or for men *trying to father* a child.

During the *first trimester* drugs may produce congenital malformations (teratogenesis), and the period of greatest risk is from the third to the eleventh week of pregnancy.

During the *second* and *third trimesters* drugs may affect the growth and functional development of the fetus or have toxic effects on fetal tissues; and drugs given shortly before term or during labour may have adverse effects on labour or on the neonate after delivery.

BNF for Children identifies drugs which:

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

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

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

Important

Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus, and all drugs should be avoided if possible during the first trimester. Drugs which have been extensively used in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs; and the smallest effective dose should be used.

Few drugs have been shown conclusively to be teratogenic in humans but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available where there is a known risk of certain defects.

Absence of information does not imply safety.

It should be noted that *BNF for Children* provides independent advice and may not always agree with the product literature.

Information on drugs and pregnancy is also available from the UK Teratology Information Service, www.uktis.org

Tel: 0844 892 0909 (09:00–17:00 Monday to Friday; urgent enquiries only outside these hours).

Prescribing in breast-feeding

Breast-feeding is beneficial; the immunological and nutritional value of breast milk to the infant is greater than that of formula feeds.

Although there is concern that drugs taken by the mother might affect the infant, there is very little information on this. In the absence of evidence of an effect, the potential for harm to the infant can be inferred from:

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

Most medicines given to a mother cause no harm to breast-fed infants and there are few contra-indications to breast-feeding when maternal medicines are necessary. However, administration of some drugs to nursing mothers can harm the infant. In the first week of life, some such as preterm or jaundiced infants are at a slightly higher risk of toxicity.

Toxicity to the infant can occur if the drug enters the milk in pharmacologically significant quantities. The concentration in milk of some drugs (e.g. fluvastatin) may exceed the concentration in maternal plasma so that therapeutic doses in the mother can cause toxicity to the infant. Some drugs inhibit the infant's sucking

reflex (e.g. phenobarbital) while others can affect lactation (e.g. bromocriptine). Drugs in breast milk may, at least theoretically, cause hypersensitivity in the infant even when concentration is too low for a pharmacological effect. *BNF for Children* identifies drugs:

- which should be used with caution or which are contra-indicated in breast-feeding for the reasons given above;
- which, on present evidence, may be given to the mother during breast-feeding, because they appear in milk in amounts which are too small to be harmful to the infant;
- which are not known to be harmful to the infant although they are present in milk in significant amounts.

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

Important

For many drugs insufficient evidence is available to provide guidance and it is advisable to administer only essential drugs to a mother during breast-feeding. Because of the inadequacy of information on drugs in breast milk information in *BNF for Children* should be used only as a guide; absence of information does not imply safety.

Prescribing in palliative care

Palliative care is the active total care of children and young adults who have incurable, life-limiting conditions and are not expected to survive beyond young adulthood.

The child may be cared for in a hospice or at home according to the needs of the child and the child's family. In all cases, children should receive total care of their physical, emotional, social, and spiritual needs, and their families should be supported throughout. In particular, specialist palliative care is essential for end-of-life care of the child and for supporting the family through death and bereavement.

Drug treatment The number of drugs should be as few as possible. Oral medication is usually appropriate unless there is severe nausea and vomiting, dysphagia, weakness, or coma, when parenteral medication may be necessary.

Pain

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

Paracetamol (p. 200) or a NSAID (p. 504) given regularly will often be sufficient to manage mild pain. If non-opioid analgesics alone are not sufficient, then an opioid analgesic alone or in combination with a non-opioid analgesic at an adequate dosage, may be helpful in the control of moderate pain. Codeine (p. 205) or tramadol (p. 212) can be considered for moderate pain. If these preparations do not control the pain then morphine (p. 208) is the most useful opioid analgesic. Alternatives to morphine, including transdermal buprenorphine (p. 205), transdermal fentanyl (p. 207), hydromorphone (p. 208), methadone (p. 208), or oxycodone (p. 210), should be initiated by those with experience in palliative care. Initiation of an opioid analgesic should not be delayed by concern over a theoretical likelihood of psychological dependence (addiction).

Bone metastases In addition to the above approach, radiotherapy and bisphosphonates, (p. 394), may be useful for pain due to bone metastases.

Neuropathic pain Patients with neuropathic pain (p. 213) may benefit from a trial of a tricyclic antidepressant, most commonly amitriptyline (p. 185), for several weeks. An antiepileptic such as carbamazepine (p. 220), may be added or substituted if pain persists. Ketamine is sometimes used under specialist supervision for neuropathic pain that responds poorly to opioid analgesics. Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone, which reduces oedema around the tumour, thus reducing compression. Nerve blocks can be considered when pain is localised to a specific area. Transcutaneous electrical nerve stimulation (TENS) may also help.

Pain management with opioids

Oral route Treatment with morphine is given by mouth as immediate-release or modified-release preparations. During the titration phase the initial dose is based on the previous medication used, the severity of the pain, and other factors such as presence of renal impairment or frailty. The dose is given either as an immediate-release preparation 4-hourly (for starting doses, see Morphine, p. 208), or as a 12-hourly modified-release preparation, in addition to rescue doses. The starting dose of 12-hourly modified-release preparations is usually 200–800 micrograms/kg every 12 hours. If replacing a weaker opioid analgesic (such as codeine), starting doses are usually higher.

If pain occurs between regular doses of morphine ('breakthrough pain'), an additional dose ('rescue dose') of immediate-release morphine should be given. An additional dose should also be given 30 minutes before an activity that causes pain, such as wound dressing. The standard dose of a strong opioid for breakthrough pain is usually one-tenth to one-sixth of the regular 24-hour dose, repeated every 2–4 hours as required (up to hourly may be needed if pain is severe or in the last days of life). Review pain management if rescue analgesic is required frequently (twice daily or more). Each child should be assessed on an individual basis. Formulations of fentanyl that are administered nasally, buccally or sublingually are not licensed for use in children; their usefulness in children is also limited by dose availability.

Children often require a higher dose of morphine in proportion to their body-weight compared to adults. Children are more susceptible to certain adverse effects of opioids such as urinary retention (which can be eased by bethanechol), and opioid-induced pruritus.

When adjusting the dose of morphine, the number of rescue doses required and the response to them should be taken into account; increments of morphine should not exceed one-third to one-half of the total daily dose every 24 hours. Thereafter, the dose should be adjusted with careful assessment of the pain, and the use of adjuvant analgesics should also be considered. Upward titration of the dose of morphine stops when either the pain is relieved or unacceptable adverse effects occur, after which it is necessary to consider alternative measures.

Once their pain is controlled, children started on 4-hourly immediate-release morphine can be transferred to the same total 24-hour dose of morphine given as the modified-release preparation for 12-hourly or 24-hourly administration. The first dose of the modified-release preparation is given with, or within 4 hours of the last dose of the immediate-release preparation. For preparations suitable for 12-hourly or 24-hourly administration see modified-release preparations under Morphine, (p. 208). Increments should be made to the dose, not to the frequency of administration. The patient must be monitored closely for efficacy and side-effects, particularly constipation, and nausea and vomiting. A suitable laxative (p. 56) should be prescribed routinely.

Oxycodone (p. 210) can be used in children who require an opioid but cannot tolerate morphine. If the child is already receiving an opioid, oxycodone should be started at a dose equivalent to the current analgesic

(see below). Oxycodone immediate-release preparations can be given for breakthrough pain.

Equivalent doses of opioid analgesics

This is only an **approximate** guide (doses may not correspond with those given in clinical practice); children should be carefully monitored after any change in medication and dose titration may be required

Analgesic	Route	Dose
Codeine	PO	100 mg
Diamorphine	IM, IV, SC	3 mg
Dihydrocodeine	PO	100 mg
Hydromorphone	PO	2 mg
Morphine	PO	10 mg
Morphine	IM, IV, SC	5 mg
Oxycodone	PO	6.6 mg
Tramadol	PO	100 mg

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

Parenteral route Diamorphine (p. 206) is preferred for injection because, being more soluble, it can be given in a smaller volume. The equivalent subcutaneous dose is approximately a third of the oral dose of morphine. Subcutaneous infusion of diamorphine via a continuous infusion device can be useful (for details, see Continuous Subcutaneous Infusions), (p. 19).

If the child can resume taking medicines by mouth, then oral morphine may be substituted for subcutaneous infusion of diamorphine. See table of Approximate Equivalent doses of Morphine and Diamorphine, (p. 20).

Rectal route Morphine is also available for rectal administration as suppositories.

Transdermal route Transdermal preparations of fentanyl (p. 207) and buprenorphine [not licensed for use in children] are available; they are not suitable for acute pain or in those children whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Prescribers should ensure that they are familiar with the correct use of transdermal preparations (see under fentanyl) because inappropriate use has caused fatalities.

The following 24-hour oral doses of morphine are considered to be *approximately* equivalent to the buprenorphine and fentanyl patches shown, however when switching due to possible opioid-induced hyperalgesia, reduce the calculated equivalent dose of the new opioid by one-quarter to one-half.

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

morphine salt 12 mg daily	≡ BuTrans® '5' patch	7-day patches
morphine salt 24 mg daily	≡ BuTrans® '10' patch	7-day patches
morphine salt 48 mg daily	≡ BuTrans® '20' patch	7-day patches
morphine salt 84 mg daily	≡ Transtec® '35' patch	4-day patches
morphine salt 126 mg daily	≡ Transtec® '52.5' patch	4-day patches
morphine salt 168 mg daily	≡ Transtec® '70' patch	4-day patches

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

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

morphine salt 30 mg daily	≡ fentanyl '12' patch
morphine salt 60 mg daily	≡ fentanyl '25' patch
morphine salt 120 mg daily	≡ fentanyl '50' patch
morphine salt 180 mg daily	≡ fentanyl '75' patch
morphine salt 240 mg daily	≡ fentanyl '100' patch

Note Fentanyl equivalences in this table are for children on well-tolerated opioid therapy for long periods, see Transdermal Route above, and section 4.7.2; fentanyl patches should not be used in opioid naïve children. Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine

Symptom control

Unlicensed indications or routes

Several recommendations in this section involve unlicensed indications or routes.

Anorexia Anorexia may be helped by prednisolone or dexamethasone.

Anxiety Anxiety can be treated with a long-acting benzodiazepine such as diazepam, or by continuous infusion of the short-acting benzodiazepine midazolam. Interventions for more acute episodes of anxiety (such as panic attacks) include short-acting benzodiazepines such as lorazepam given sublingually or midazolam given subcutaneously. Temazepam provides useful night-time sedation in some children.

Capillary bleeding Capillary bleeding can be treated with tranexamic acid (p. 121) by mouth; treatment is usually continued for one week after the bleeding has stopped but it can be continued at a reduced dose if bleeding persists. Alternatively, gauze soaked in tranexamic acid 100 mg/mL or adrenaline (epinephrine) solu-

tion 1 mg/mL (1 in 1000) can be applied to the affected area.

Vitamin K may be useful for the treatment and prevention of bleeding associated with prolonged clotting in liver disease. In severe chronic cholestasis, absorption of vitamin K may be impaired; either parenteral or water-soluble oral vitamin K should be considered (section 9.6.6).

Constipation Constipation is a common cause of distress and is almost invariable after administration of an opioid analgesic. It should be prevented if possible by the regular administration of laxatives. Suitable laxatives include osmotic laxatives (p. 61) (such as lactulose or macrogols), stimulant laxatives (p. 58) (such as co-danthramer and senna) or the combination of lactulose and a senna preparation. Naloxone given by mouth may help relieve opioid-induced constipation; it is poorly absorbed but opioid withdrawal reactions have been reported.

Convulsions Intractable seizures are relatively common in children dying from non-malignant conditions. Phenobarbital by mouth or as a continuous subcutaneous infusion may be beneficial; continuous infusion of midazolam is an alternative. Both cause drowsiness, but this is rarely a concern in the context of intractable seizures. For breakthrough convulsions diazepam (p. 236) given rectally (as a solution), buccal midazolam (p. 238), or paraldehyde (p. 238) as an enema may be appropriate.

For the use of midazolam by subcutaneous infusion using a continuous infusion device, see p. 19.

Dry mouth Dry mouth may be caused by certain medications including opioid analgesics, antimuscarinic drugs (e.g. hyoscine), antidepressants and some anti-emetics; if possible, an alternative preparation should be considered. Dry mouth may be relieved by good mouth care and measures such as chewing sugar-free gum, sucking ice or pineapple chunks, or the use of artificial saliva (p. 554); dry mouth associated with candidiasis can be treated by oral preparations of nystatin (p. 552) or miconazole (p. 552); alternatively, fluconazole (p. 305) can be given by mouth.

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

Dyspnoea Breathlessness at rest may be relieved by regular oral morphine in carefully titrated doses. Diazepam may be helpful for dyspnoea associated with anxiety. Sublingual lorazepam or subcutaneous or buccal midazolam are alternatives. A nebulised short-acting β_2 agonist (section 3.1.1.1) or a corticosteroid (section 3.2), such as dexamethasone or prednisolone, may also be helpful for bronchospasm or partial obstruction.

Excessive respiratory secretion Excessive respiratory secretion (death rattle) may be reduced by hyoscine hydrobromide patches (p. 198) or by subcutaneous or intravenous injection of hyoscine hydrobromide 10 micrograms/kg (max. 600 micrograms) every 4 to 8 hours; however, care must be taken to avoid the discomfort of dry mouth. Alternatively, glycopyrronium (p. 641) may be given.

For the administration of hyoscine hydrobromide by subcutaneous or intravenous infusion using a continuous infusion device, see p. 19.

Fungating tumours Fungating tumours can be treated by regular dressing and antibacterial drugs; systemic treatment with metronidazole (p. 299) is often required to reduce malodour, but topical metronidazole (p. 593) is also used.

Gastro-intestinal pain The pain of bowel colic may be reduced by loperamide (p. 46). Hyoscine hydrobromide (p. 198) may also be helpful in reducing the frequency of spasms; it is given sublingually at a dose of 10 micrograms/kg (max. 300 micrograms) 3 times daily as *Kwells*[®] tablets. For the dose by subcutaneous infusion, see p. 19.

Gastric distension pain due to pressure on the stomach may be helped by a preparation incorporating an antacid with an antiflatulent (p. 35) and a prokinetic such as domperidone before meals.

Hiccup Hiccup due to gastric distension may be helped by a preparation incorporating an antacid with an antiflatulent (p. 35).

Hypercalcaemia See section 9.5.1.2.

Insomnia Children with advanced cancer may not sleep because of discomfort, cramps, night sweats, joint stiffness, or fear. There should be appropriate treatment of these problems before hypnotics (p. 168) are used. Benzodiazepines, such as temazepam, may be useful.

Intractable cough Intractable cough may be relieved by moist inhalations or by regular administration of oral morphine every 4 hours. Methadone linctus should be avoided because it has a long duration of action and tends to accumulate.

Mucosal bleeding Mucosal bleeding from the mouth and nose occurs commonly in the terminal phase, particularly in a child suffering from haemopoietic malignancy. Bleeding from the nose caused by a single bleeding point can be arrested by cauterisation or by dressing it. Tranexamic acid (p. 121) may be effective applied topically or given systemically.

Muscle spasm The pain of muscle spasm can be helped by a muscle relaxant such as diazepam (p. 521) or baclofen (p. 520).

Nausea and vomiting Nausea and vomiting are common in children with advanced cancer. Ideally, the cause should be determined before treatment with an antiemetic (section 4.6) is started.

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

Metoclopramide has a prokinetic action and is used by mouth for nausea and vomiting associated with gastritis, gastric stasis, and functional bowel obstruction. Drugs with antimuscarinic effects antagonise prokinetic drugs and, if possible, should not therefore be used concurrently.

Haloperidol (p. 174) is used by mouth or by continuous intravenous or subcutaneous infusion for most metab-

olic causes of vomiting (e.g. hypercalcaemia, renal failure).

Cyclizine (p. 194) is used for nausea and vomiting due to mechanical bowel obstruction, raised intracranial pressure, and motion sickness.

Ondansetron (p. 197) is most effective when the vomiting is due to damaged or irritated gut mucosa (e.g. after chemotherapy or radiotherapy).

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

Levomepromazine (p. 175) can be used if first-line antiemetics are inadequate. Dexamethasone by mouth can be used as an adjunct.

For the administration of antiemetics by subcutaneous infusion using a continuous infusion device, see below.

For the treatment of nausea and vomiting associated with cancer chemotherapy, see section 8.1.

Pruritus Pruritus, even when associated with obstructive jaundice, often responds to simple measures such as application of emollients (p. 558). Ondansetron may be effective in some children. Where opioid analgesics cause pruritus it may be appropriate to review the dose or to switch to an alternative opioid analgesic. In the case of obstructive jaundice, further measures include administration of colestyramine (p. 69).

Raised intracranial pressure Headache due to raised intracranial pressure often responds to a high dose of a corticosteroid, such as dexamethasone, for 4 to 5 days, subsequently reduced if possible; dexamethasone should be given before 6 p.m. to reduce the risk of insomnia. Treatment of headache and of associated nausea and vomiting should also be considered.

Restlessness and confusion Restlessness and confusion may require treatment with haloperidol (p. 174) 10–20 micrograms/kg by mouth every 8–12 hours. Levomepromazine (p. 175) is also used occasionally for restlessness. See also below.

Continuous subcutaneous infusions

Although drugs can usually be administered *by mouth* to control symptoms in palliative care, the parenteral route may sometimes be necessary. Repeated administration of *intramuscular injections* should be avoided in children, particularly if cachectic. This has led to the use of portable continuous infusion devices such as syringe drivers to give a *continuous subcutaneous infusion*, which can provide good control of symptoms with little discomfort or inconvenience to the patient.

Syringe driver rate settings

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

Indications for the **parenteral route** are:

- inability to take medicines by mouth owing to *nausea and vomiting, dysphagia, severe weakness, or coma*;

- *malignant bowel obstruction* for which surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube);
- refusal by the child to take regular medication by mouth.

Bowel colic and excessive respiratory secretions Hyoscine hydrobromide (p. 198) effectively reduces respiratory secretions and is sedative (but occasionally causes paradoxical agitation); it is given in a *subcutaneous or intravenous infusion* dose of 40–60 micrograms/kg/24 hours. Glycopyrronium (p. 641) may also be used.

Hyoscine butylbromide (p. 38) is effective in bowel colic, is less sedative than hyoscine hydrobromide, but is not always adequate for the control of respiratory secretions; it is given by *subcutaneous infusion* (**important**: *hyoscine butylbromide* must not be confused with *hyoscine hydrobromide*, above).

Confusion and restlessness Haloperidol has little sedative effect. Levomepromazine (p. 175) has a sedative effect. Midazolam is a sedative and an antiepileptic that may be suitable for a very restless patient.

Convulsions If a child has previously been receiving an antiepileptic drug or has a primary or secondary cerebral tumour or is at risk of convulsion (e.g. owing to uraemia) antiepileptic medication should not be stopped. Midazolam (p. 238) is the benzodiazepine antiepileptic of choice for *continuous subcutaneous infusion*.

Prescribing of midazolam in palliative care

The use of high strength midazolam (5 mg/mL in 2 mL and 10 mL ampoules, or 2 mg/mL in 5 mL ampoules) should be considered in palliative care, and other situations where a higher strength may be more appropriate to administer the prescribed dose, and where the risk of overdosage has been assessed. It is advised that flumazenil (section 15.1.7) is available where midazolam is used, to reverse the effects if necessary.

Nausea and vomiting Levomepromazine (p. 175) causes sedation in about 50% of patients. Haloperidol (p. 174) has little sedative effect.

Cyclizine (p. 194) is particularly likely to precipitate if mixed with diamorphine or other drugs (see under *Mixing and Compatibility*); it is given by *subcutaneous infusion*.

Pain control Diamorphine (p. 206) is the preferred opioid since its high solubility permits a large dose to be given in a small volume (see under *Mixing and Compatibility*). The table on p. 20 shows approximate equivalent doses of morphine and diamorphine.

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

In theory injections dissolved in water for injections are more likely to be associated with pain (possibly owing to

their hypotonicity). The use of physiological saline (sodium chloride 0.9%) however increases the likelihood of precipitation when more than one drug is used; moreover subcutaneous infusion rates are so slow (0.1–0.3 mL/hour) that pain is not usually a problem when water is used as a diluent.

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

The following can be mixed with *diamorphine*:

Cyclizine ¹	Hyoscine hydrobromide
Dexamethasone ²	Levomopromazine
Haloperidol ³	Metoclopramide ⁴
Hyoscine butylbromide	Midazolam

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

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

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

Equivalent doses of morphine sulfate and diamorphine hydrochloride given over 24 hours

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

MORPHINE		PARENTERAL DIAMORPHINE
Oral morphine sulfate	Subcutaneous infusion of morphine sulfate	Subcutaneous infusion of diamorphine hydrochloride
over 24 hours	over 24 hours	over 24 hours
30 mg	15 mg	10 mg
60 mg	30 mg	20 mg
90 mg	45 mg	30 mg
120 mg	60 mg	40 mg
180 mg	90 mg	60 mg
240 mg	120 mg	80 mg
360 mg	180 mg	120 mg
480 mg	240 mg	160 mg
600 mg	300 mg	200 mg
780 mg	390 mg	260 mg
960 mg	480 mg	320 mg
1200 mg	600 mg	400 mg

If breakthrough pain occurs give a subcutaneous injection equivalent to one-tenth to one-sixth of the total 24-hour subcutaneous infusion dose. With an intermittent subcutaneous injection absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle).
To minimise the risk of infection no subcutaneous infusion solution should be used for longer than 24 hours.

1. Cyclizine may precipitate at concentrations above 10 mg/mL or in the presence of sodium chloride 0.9% or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also likely to precipitate after 24 hours.
2. Special care is needed to avoid precipitation of dexamethasone when preparing it.
3. Mixtures of haloperidol and diamorphine are likely to precipitate after 24 hours if haloperidol concentration is above 2 mg/mL.
4. Under some conditions, infusions containing metoclopramide become discoloured; such solutions should be discarded.

Prescribing in dental practice

Advice on the drug management of dental and oral conditions is covered in the main text. For ease of access, guidance on such conditions is usually identified by means of a relevant heading (e.g. Dental and Orofacial Pain) in the appropriate sections.

The following is a list of topics of particular relevance to dentists.

General guidance

- Prescribing by dentists, see BNF
- Oral side-effects of drugs, see BNF
- Medical emergencies in dental practice, see BNF

Medical problems in dental practice, see BNF

Drug management of dental and oral conditions

Dental and orofacial pain, p. 199

- Neuropathic pain, p. 213
- Non-opioid analgesics and compound analgesic preparations, p. 199
- Opioid analgesics, p. 205
- Non-steroidal anti-inflammatory drugs, p. 505

Oral infections

- Bacterial infections, p. 247
 - Phenoxymethylpenicillin, p. 262
 - Broad-spectrum penicillins (amoxicillin and ampicillin), p. 265
 - Cephalosporins (cefalexin and cefradine), p. 270
 - Tetracyclines, p. 277
 - Macrolides (clarithromycin, erythromycin and azithromycin), p. 284
 - Clindamycin, p. 287
 - Metronidazole, p. 299
 - Fusidic acid p. 593
- Fungal infections, p. 551
 - Local treatment, p. 551
 - Systemic treatment, p. 304
- Viral infections, p. 551
 - Herpetic gingivostomatitis, local treatment, p. 551
 - Herpetic gingivostomatitis, systemic treatment, p. 325 and p. 551
 - Herpes labialis, p. 597

Anaesthetics, anxiolytics and hypnotics

- Anaesthesia, sedation, and resuscitation in dental practice, p. 635
- Hypnotics, p. 169
- Sedation for dental procedures, p. 642
- Local anaesthesia, p. 655

Oral ulceration and inflammation, p. 549

Mouthwashes and gargles, p. 553

Dry mouth, p. 554

Minerals

- Fluorides, p. 482

Aromatic inhalations, p. 166

Nasal decongestants, p. 548

Dental Practitioners' Formulary, p. 826

Drugs and sport

UK Anti-Doping, the national body responsible for the UK's anti-doping policy, advises that athletes are personally responsible should a prohibited substance be detected in their body. An advice card listing examples of permitted and prohibited substances is available from:

UK Anti-Doping
Oceanic House
1a Cockspur Street
London SW1Y 5BG
Tel: (020) 7766 7350
information@ukad.org.uk
www.ukad.org.uk

General Medical Council's advice

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

Emergency treatment of poisoning

These notes provide only an overview of the treatment of poisoning and it is strongly recommended that either **TOXBASE** or the **UK National Poisons Information Service** (see below) be consulted when there is doubt about the degree of risk or about appropriate management.

Most childhood poisoning is accidental. Other causes include intentional overdose, drug abuse, iatrogenic and deliberate poisoning. The drugs most commonly involved in childhood poisoning are paracetamol, ibuprofen, orally ingested creams, aspirin, iron preparations, cough medicines, and the contraceptive pill.

Hospital admission Children who have features of poisoning should generally be admitted to hospital. Children who have taken poisons with delayed actions should also be admitted, even if they appear well. Delayed-action poisons include aspirin, iron, paracetamol, tricyclic antidepressants, and co-phenotrope (diphenoxylate with atropine, *Lomotil*®); the effects of modified-release preparations are also delayed. A note of all relevant information, including what treatment has been given, should accompany the patient to hospital.

Further information and advice

TOXBASE, the primary clinical toxicology database of the National Poisons Information Service, is available on the Internet to registered users at www.toxbase.org (a backup site is available at www.toxbasebackup.org if the main site cannot be accessed). It provides information about routine diagnosis, treatment, and management of patients exposed to drugs, household products, and industrial and agricultural chemicals.

Specialist information and advice on the treatment of poisoning is available day and night from the **UK National Poisons Information Service** on the following number:

Tel: 0844 892 0111

Advice on laboratory analytical services can be obtained from **TOXBASE** or from the National Poisons Information Service.

Help with identifying capsules or tablets may be available from a regional medicines information centre (see inside front cover) or (out of hours) from the National Poisons Information Service.

General care

It is often impossible to establish with certainty the identity of the poison and the size of the dose. This is not usually important because only a few poisons (such as opioids, paracetamol, and iron) have specific antidotes; few children require active removal of the poison. In most children, treatment is directed at managing symptoms as they arise. Nevertheless, knowledge of the type and timing of poisoning can help in anticipating the course of events. All relevant information should be sought from the poisoned child and from their carers.

However, such information should be interpreted with care because it may not be complete or entirely reliable. Sometimes symptoms arise from other illnesses, and children should be assessed carefully. Accidents may involve a number of domestic and industrial products (the contents of which are not generally known). The **National Poisons Information Service** should be consulted when there is doubt about any aspect of suspected poisoning.

Respiration

Respiration is often impaired in unconscious children. An obstructed airway requires immediate attention. In the absence of trauma, the airway should be opened with simple measures such as chin lift or jaw thrust. An oropharyngeal or nasopharyngeal airway may be useful in children with reduced consciousness to prevent obstruction, provided ventilation is adequate. Intubation and ventilation should be considered in children whose airway cannot be protected or who have respiratory acidosis because of inadequate ventilation; such children should be monitored in a critical care area.

Most poisons that impair consciousness also depress respiration. Assisted ventilation (either mouth-to-mouth or using a bag-valve-mask device) may be needed. Oxygen is not a substitute for adequate ventilation, although it should be given in the highest concentration possible in poisoning with carbon monoxide and irritant gases.

The potential for pulmonary aspiration of gastric contents should be considered.

Blood pressure

Hypotension is common in severe poisoning with central nervous system depressants; if severe, this may lead to irreversible brain damage or renal tubular necrosis. Hypotension should be corrected initially by raising the foot of the bed and administration of either sodium chloride intravenous infusion or a colloidal infusion. Vasoconstrictor sympathomimetics (section 2.7.2) are rarely required and their use may be discussed with a paediatric intensive care unit.

Fluid depletion without hypotension is common after prolonged coma and after aspirin poisoning due to vomiting, sweating, and hyperpnoea.

Hypertension, often transient, occurs less frequently than hypotension in poisoning; it may be associated with sympathomimetic drugs such as amfetamines, phencyclidine, and cocaine.

Heart

Cardiac conduction defects and arrhythmias can occur in acute poisoning, notably with tricyclic antidepressants, some antipsychotics, and some antihistamines. Arrhythmias often respond to correction of underlying hypoxia, acidosis, or other biochemical abnormalities, but ventricular arrhythmias that cause serious hypo-

tension may require treatment (section 2.3.1). If the QT interval is prolonged, specialist advice should be sought because the use of some anti-arrhythmic drugs may be inappropriate. Supraventricular arrhythmias are seldom life-threatening and drug treatment is best withheld until the child reaches hospital.

Body temperature

Hypothermia may develop in patients of any age who have been deeply unconscious for some hours, particularly following overdose with barbiturates or phenothiazines. It may be missed unless core temperature is measured using a low-reading rectal thermometer or by some other means. Hypothermia should be managed by prevention of further heat loss and appropriate re-warming as clinically indicated.

Hyperthermia can develop in children taking CNS stimulants; children are also at risk when taking therapeutic doses of drugs with antimuscarinic properties. Hyperthermia is initially managed by removing all unnecessary clothing and using a fan. Sponging with tepid water will promote evaporation. Advice should be sought from the National Poisons Information Service on the management of severe hyperthermia resulting from conditions such as the serotonin syndrome.

Both hypothermia and hyperthermia require urgent hospitalisation for assessment and supportive treatment.

Convulsions

Single short-lived convulsions (lasting less than 5 minutes) do not require treatment. If convulsions are protracted or recur frequently, lorazepam 100 micrograms/kg (max. 4 mg) or diazepam (preferably as emulsion) 300–400 micrograms/kg (max. 10 mg) should be given by slow intravenous injection into a large vein. Benzodiazepines should not be given by the intramuscular route for convulsions. If the intravenous route is not readily available, midazolam can be given by the buccal route or diazepam can be administered as a rectal solution (section 4.8.2).

Methaemoglobinaemia

Drug- or chemical-induced methaemoglobinaemia should be treated with **methylthioninium chloride** if the methaemoglobin concentration is 30% or higher, or if symptoms of tissue hypoxia are present despite oxygen therapy. Methylthioninium chloride reduces the ferric iron of methaemoglobin back to the ferrous iron of haemoglobin; in high doses, methylthioninium can itself cause methaemoglobinaemia.

METHYLTHIONINIUM CHLORIDE (Methylene blue)

Cautions children under 3 months more susceptible to methaemoglobinaemia from high doses of methylthioninium; G6PD deficiency (seek advice from National Poisons Information Service); chlorate poisoning (reduces efficacy of methylthioninium); methaemoglobinaemia due to treatment of cyanide poisoning with sodium nitrite (seek advice from National Poisons Information Service); pulse oximetry may give false estimation of oxygen saturation; **interactions:** Appendix 1 (methylthioninium)

Renal impairment use with caution in severe impairment (dose reduction may be required)

Pregnancy no information available, but risk to fetus of untreated methaemoglobinaemia likely to be significantly higher than risk of treatment

Breast-feeding manufacturer advises avoid breastfeeding for up to 6 days after administration—no information available

Side-effects nausea, vomiting, abdominal pain, hyperbilirubinaemia (in infants), chest pain, arrhythmia, hypertension, hypotension, dyspnoea, tachypnoea, headache, dizziness, tremor, confusion, anxiety, agitation, fever, haemolytic anaemia, methaemoglobinaemia, blue-green discoloration of urine, faeces, and skin, mydriasis, sweating

Indications and dose

Drug- or chemical-induced methaemoglobin-aemia (see notes above)

• By slow intravenous injection over 5 minutes

Neonate seek advice from National Poisons Information Service

Child 1–3 months seek advice from National Poisons Information Service

Child 3 months–18 years 1–2 mg/kg, repeated after 30–60 minutes if necessary; seek advice from National Poisons Information Service if further repeat doses required (max. cumulative dose per course 7 mg/kg, or if aniline- or dapsone-induced methaemoglobinaemia, 4 mg/kg)

Administration for intravenous injection, may be diluted with Glucose 5% to minimise injection-site pain; not compatible with Sodium Chloride 0.9%

Proveblue® (Martindale) (PmM)

Injection, methylthioninium chloride 5 mg/mL, net price 10-mL amp = £39.38

Removal and elimination

Prevention of absorption Given by mouth, activated charcoal can adsorb many poisons in the gastro-intestinal system, thereby reducing their absorption. The sooner it is given the more effective it is, but it may still be effective up to 1 hour after ingestion of the poison—longer in the case of modified-release preparations or of drugs with antimuscarinic (anticholinergic) properties. It is particularly useful for the prevention of absorption of poisons that are toxic in small amounts such as antidepressants.

A second dose may occasionally be required when blood-drug concentration continues to rise suggesting delayed drug release or delayed gastric emptying.

For the use of charcoal in active elimination techniques, see below.

Active elimination techniques Repeated doses of activated charcoal by mouth may enhance the elimination of some drugs after they have been absorbed; repeated doses are given after overdosage with:

Carbamazepine
Dapsone
Phenobarbital
Quinine
Theophylline

Vomiting should be treated (e.g. with an antiemetic drug) since it may reduce the efficacy of charcoal treatment. In cases of intolerance, the dose may be

reduced and the frequency increased but this may compromise efficacy.

Other techniques intended to enhance the elimination of poisons after absorption are only practicable in hospital and are only suitable for a small number of severely poisoned patients. Moreover, they only apply to a limited number of poisons. Examples include:

- haemodialysis for ethylene glycol, lithium, methanol, phenobarbital, salicylates, and sodium valproate
- alkalinisation of the urine for salicylates.

Removal from the gastro-intestinal tract Gastric lavage is rarely required as benefit rarely outweighs risk; advice should be sought from the National Poisons Information Service if a significant quantity of iron or lithium has been ingested within the previous hour.

Whole bowel irrigation (by means of a bowel cleansing preparation) has been used in poisoning with certain modified-release or enteric-coated formulations, in severe poisoning with lithium salts, and if illicit drugs are carried in the gastro-intestinal tract ('body-packing'). However, it is not clear that the procedure improves outcome and advice should be sought from the National Poisons Information Service.

The administration of **laxatives** alone has no role in the management of the poisoned child and is not a recommended method of gut decontamination. The routine use of a laxative in combination with activated charcoal has mostly been abandoned. Laxatives should not be administered to young children because of the likelihood of fluid and electrolyte imbalance.

CHARCOAL, ACTIVATED

Cautions drowsy or comatose child (risk of aspiration—ensure airway protected); reduced gastro-intestinal motility (risk of obstruction); **not** for poisoning with petroleum distillates, corrosive substances, alcohols, malathion, cyanides, and metal salts including iron and lithium salts

Side-effects black stools

Indications and dose

Reduction of absorption of poisons

- By mouth

Neonate 1 g/kg

Child 1 month–12 years 1 g/kg (max. 50 g)

Child 12–18 years 50 g

Active elimination of poisons

- By mouth

Neonate 1 g/kg every 4 hours

Child 1 month–12 years 1 g/kg (max. 50 g) every 4 hours

Child 12–18 years 50 g every 4 hours

Administration suspension or reconstituted powder may be mixed with soft drinks (e.g. caffeine-free diet cola) or fruit juices to mask the taste

Actidose-Aqua® Advance (Alliance)

Oral suspension, activated charcoal 1.04 g/5 mL, net price 50-g pack (240 mL) = £12.89

Carbomix® (Beacon)

Granules, activated charcoal, net price 50-g pack = £11.90

Charcodote® (TEVA UK)

Oral suspension, activated charcoal 1 g/5 mL, net price 50-g pack = £11.88

Specific drugs

Alcohol

Features of acute intoxication with alcohol (ethanol) in children include ataxia, dysarthria, nystagmus, and drowsiness, which may progress to coma, with hypotension and acidosis. Aspiration of vomit is a special hazard and hypoglycaemia may occur. Patients are managed supportively, with particular attention to maintaining a clear airway and measures to reduce the risk of aspiration of gastric contents. The blood glucose is measured and glucose given if indicated.

The **National Poisons Information Service** (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

Analgesics (non-opioid)

Aspirin The main features of salicylate poisoning are hyperventilation, tinnitus, deafness, vasodilatation, and sweating. Coma is uncommon but indicates very severe poisoning. The associated acid-base disturbances are complex.

Treatment must be in hospital, where plasma salicylate, pH, and electrolytes (particularly potassium) can be measured; absorption of aspirin may be slow and the plasma-salicylate concentration may continue to rise for several hours, requiring repeated measurement. Plasma-salicylate concentration may not correlate with clinical severity in children, and clinical and biochemical assessment is necessary. Generally, the clinical severity of poisoning is less below a plasma-salicylate concentration of 500 mg/litre (3.6 mmol/litre) unless there is evidence of metabolic acidosis. Activated charcoal should be given within 1 hour of ingesting more than 125 mg/kg aspirin. Fluid losses should be replaced and intravenous sodium bicarbonate may be given (ensuring plasma-potassium concentration is maintained within the reference range) to enhance urinary salicylate excretion (optimum urinary pH 7.5–8.5); treatment should be given in a high dependency unit.

Plasma-potassium concentration should be corrected before giving sodium bicarbonate as hypokalaemia may complicate alkalinisation of the urine.

Haemodialysis is the treatment of choice for severe salicylate poisoning and should be considered when the plasma-salicylate concentration exceeds 700 mg/litre (5.1 mmol/litre) or in the presence of severe metabolic acidosis, convulsions, renal failure, pulmonary oedema or persistently high plasma-salicylate concentrations unresponsive to urinary alkalinisation.

NSAIDs Mefenamic acid has important consequences in overdosage because it can cause convulsions, which if prolonged or recurrent, require treatment with intravenous lorazepam or diazepam.

Overdosage with ibuprofen may cause nausea, vomiting, epigastric pain, and tinnitus, but more serious toxicity is very uncommon. Activated charcoal followed by symptomatic measures are indicated if more than 100 mg/kg has been ingested within the preceding hour.

Paracetamol

In cases of **intravenous paracetamol** poisoning contact the National Poisons Information Service for advice on risk assessment and management.

Toxic doses of paracetamol may cause severe hepatocellular necrosis and, much less frequently, renal tubular necrosis. Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of right subcostal pain and tenderness, usually indicates development of hepatic necrosis. Liver damage is maximal 3–4 days after paracetamol overdose and may lead to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Therefore, despite a lack of significant early symptoms, children who have taken an overdose of paracetamol should be transferred to hospital urgently.

To avoid underestimating the potentially toxic paracetamol dose ingested by obese children who weigh more than 110 kg, use a body-weight of 110 kg (rather than their actual body-weight) when calculating the total dose of paracetamol ingested (in mg/kg).

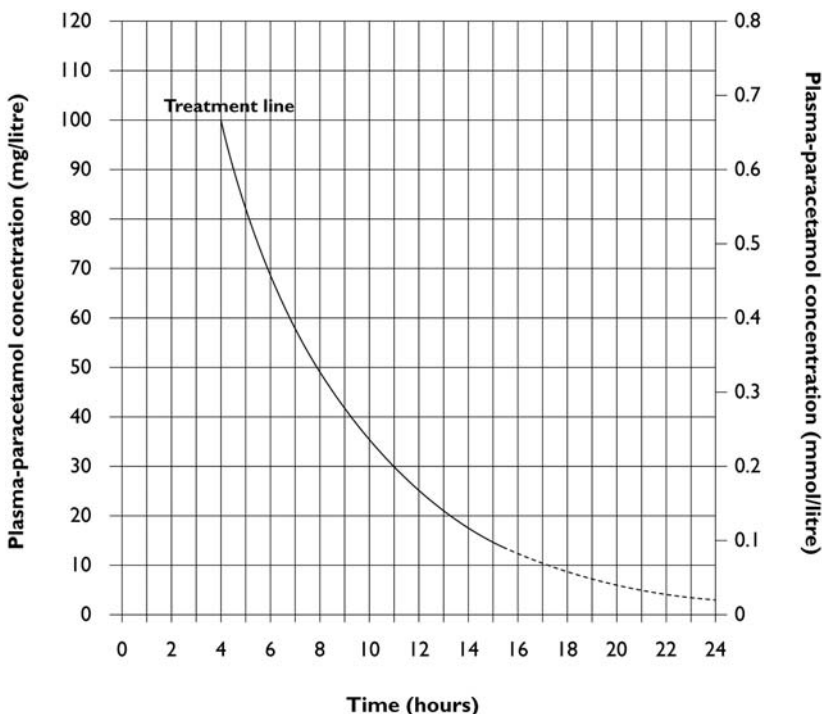
Acetylcysteine protects the liver if infused up to, and possibly beyond, 24 hours of ingesting paracetamol. It is most effective if given within 8 hours of ingestion, after

which effectiveness declines. Very rarely, giving acetylcysteine by mouth [unlicensed route] is an alternative if intravenous access is not possible—contact the National Poisons Information Service for advice.

Neonates less than 45 weeks corrected gestational age may be more susceptible to paracetamol-induced liver toxicity, therefore, treatment with acetylcysteine should be considered in all paracetamol overdoses, and advice should be sought from the National Poisons Information Service.

Acute overdose Hepatotoxicity may occur after a single ingestion of more than 150 mg/kg paracetamol taken in less than 1 hour. Rarely, hepatotoxicity may develop with single ingestions as low as 75 mg/kg of paracetamol taken in less than 1 hour. Children who have ingested 75 mg/kg or more of paracetamol in less than 1 hour should be referred to hospital. Administration of activated charcoal should be considered if paracetamol in excess of 150 mg/kg is thought to have been ingested within the previous hour.

Children at risk of liver damage and, therefore, requiring acetylcysteine, can be identified from a single measurement of the plasma-paracetamol concentration, related to the time from ingestion, provided this time interval is not less than 4 hours; earlier samples may be misleading. The concentration is plotted on a paracetamol treatment graph, with a reference line ('treatment



Patients whose plasma-paracetamol concentrations are on or above the **treatment line** should be treated with acetylcysteine by intravenous infusion.

The prognostic accuracy after 15 hours is uncertain, but a plasma-paracetamol concentration on or above the treatment line should be regarded as carrying a serious risk of liver damage.

Graph reproduced courtesy of Medicines and Healthcare products Regulatory Agency

line') joining plots of 100 mg/litre (0.66 mmol/litre) at 4 hours and 3.13 mg/litre (0.02 mmol/litre) at 24 hours (see p. 27). Acetylcysteine treatment should commence immediately in children:

- whose plasma-paracetamol concentration falls on or above the *treatment line* on the paracetamol treatment graph (see p. 27);
- who present 8–24 hours after taking an acute overdose of more than 150 mg/kg of paracetamol, even if the plasma-paracetamol concentration is not yet available; acetylcysteine can be discontinued if the plasma-paracetamol concentration is later reported to be below the *treatment line* on the paracetamol treatment graph (see p. 27), provided that the child is asymptomatic and liver function tests, serum creatinine and INR are normal.

The prognostic accuracy of a plasma-paracetamol concentration taken after 15 hours is uncertain, but a concentration on or above the *treatment line* on the paracetamol treatment graph (see p. 27) should be regarded as carrying a serious risk of liver damage. If more than 15 hours have elapsed since ingestion, or there is doubt about appropriate management, advice should be sought from the National Poisons Information Service.

'Staggered' overdose, uncertain time of overdose, or therapeutic excess A 'staggered' overdose involves ingestion of a potentially toxic dose of paracetamol over more than one hour, with the possible intention of causing self-harm. Therapeutic excess is the inadvertent ingestion of a potentially toxic dose of paracetamol during its clinical use. The paracetamol treatment graph is unreliable if a 'staggered' overdose is taken, if there is uncertainty about the time of the overdose, or if there is therapeutic excess. In these cases, children who have taken more than 150 mg/kg of paracetamol in any 24-hour period are at risk of toxicity and should be commenced on acetylcysteine immediately, unless it is more than 24 hours since the last ingestion, the patient is asymptomatic, the plasma-paracetamol concentration is undetectable, and liver function tests, serum creatinine and INR are normal.

Rarely, toxicity can occur with paracetamol doses between 75–150 mg/kg in any 24-hour period; for some children this may be within the licensed dose, but ingestion of a licensed dose of paracetamol is not considered an overdose. Clinical judgement of the individual case is necessary to determine whether to treat those who have ingested this amount of paracetamol.

Although there is some evidence suggesting that factors such as the use of liver enzyme-inducing drugs (e.g. carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin, St John's wort), chronic alcoholism, and starvation may increase the risk of hepatotoxicity, the CHM has advised that these should no longer be used in the assessment of paracetamol toxicity.

Significant toxicity is unlikely if, 24 hours or longer after the last paracetamol ingestion, the patient is asymptomatic, the plasma-paracetamol concentration is undetectable, and liver function tests, serum creatinine and INR are normal. Children with clinical features of hepatic injury such as jaundice or hepatic tenderness should be treated urgently with acetylcysteine. If there is uncertainty about a patient's risk of toxicity after paracetamol overdose, treatment with acetylcysteine should be commenced. Advice should be sought from

the National Poisons Information Service whenever necessary.

The **National Poisons Information Service** (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

ACETYLACETALDEHYDE

Cautions atopy, asthma (see Side-effects below, but do not delay acetylcysteine treatment); acetylcysteine may mildly increase INR and prothrombin time

Side-effects hypersensitivity-like reactions managed by reducing infusion rate or suspending until reaction settled (rash also managed by giving antihistamine; acute asthma managed by giving nebulised short-acting beta₂ agonist)—contact the National Poisons Information Service if reaction severe; mild increase in INR and prothrombin time

Indications and dose

Paracetamol overdose see notes above

• By intravenous infusion

Neonate initially 150 mg/kg in 3 mL/kg glucose 5% and given over 1 hour, followed by 50 mg/kg in 7 mL/kg glucose 5% and given over 4 hours, then 100 mg/kg in 14 mL/kg glucose 5% and given over 16 hours

Child 1 month–18 years

Body-weight under 20 kg initially 150 mg/kg in 3 mL/kg glucose 5% and given over 1 hour, followed by 50 mg/kg in 7 mL/kg glucose 5% and given over 4 hours, then 100 mg/kg in 14 mL/kg glucose 5% and given over 16 hours

Body-weight 20–40 kg initially 150 mg/kg in 100 mL glucose 5% and given over 1 hour, followed by 50 mg/kg in 250 mL glucose 5% and given over 4 hours, then 100 mg/kg in 500 mL glucose 5% and given over 16 hours

Body-weight over 40 kg see Acetylcysteine Dose and Administration in the *BNF*

Note Glucose 5% is preferred infusion fluid; Sodium Chloride 0.9% is an alternative if Glucose 5% unsuitable

Acetylcysteine (Non-proprietary) (PoM)

Concentrate for intravenous infusion, acetylcysteine 200 mg/mL, net price 10-mL amp = £1.96

Parvolex® (UCB Pharma) (PoM)

Concentrate for intravenous infusion, acetylcysteine 200 mg/mL, net price 10-mL amp = £2.25

Electrolytes Na⁺ 14 mmol/10-mL amp

Analgesics (opioid)

Opioids (narcotic analgesics) cause varying degrees of coma, respiratory depression, and pinpoint pupils. The specific antidote **naloxone** is indicated if there is coma or bradypnoea. Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. When repeated administration of naloxone is required, it can be given by continuous intravenous infusion instead and the rate of infusion adjusted according to vital signs. All children should be observed for at least 6 hours after the last dose of naloxone. The effects of some opioids, such as buprenorphine, are only partially reversed by naloxone.

Dextropropoxyphene and methadone have very long durations of action; patients may need to be monitored for long periods following large overdoses.

Naloxone reverses the opioid effects of dextropropoxyphene; the long duration of action of dextropropoxyphene calls for prolonged monitoring and further doses of naloxone may be required. Norpropoxyphene, a metabolite of dextropropoxyphene, also has cardiotoxic effects which may require treatment with **sodium bicarbonate**, or **magnesium sulfate**, or both; arrhythmias may occur for up to 12 hours.

NALOXONE HYDROCHLORIDE

Cautions physical dependence on opioids; cardiac irritability; naloxone is short-acting, see notes above

Pregnancy section 15.1.7

Breast-feeding section 15.1.7

Indications and dose

Safe Practice

Doses used in acute opioid overdosage may not be appropriate for the management of opioid-induced respiratory depression and sedation in those receiving palliative care and in chronic opioid use; see also section 15.1.7 for management of postoperative respiratory depression

Overdosage with opioids

• By intravenous injection

Neonate 100 micrograms/kg; if no response, repeat at intervals of 1 minute to a total max. 2 mg, then review diagnosis; further doses may be required if respiratory function deteriorates

Child 1 month–12 years 100 micrograms/kg (max. 2 mg); if no response, repeat at intervals of 1 minute to a total max. 2 mg, then review diagnosis; further doses may be required if respiratory function deteriorates

Child 12–18 years 400 micrograms; if no response after 1 minute, give 800 micrograms, and if still no response after another 1 minute, repeat dose of 800 micrograms; if still no response, give 2 mg (4 mg may be required in a seriously poisoned patient), then review diagnosis; further doses may be required if respiratory function deteriorates

• By subcutaneous or intramuscular injection

As intravenous injection but only if intravenous route not feasible (onset of action slower)

• By continuous intravenous infusion using an infusion pump

Neonate rate adjusted according to response (initially, rate may be set at 60% of the initial resuscitative *intravenous injection* dose per hour)

Child 1 month–18 years rate adjusted according to response (initially, rate may be set at 60% of the initial resuscitative *intravenous injection* dose per hour)

Note The initial resuscitative *intravenous injection* dose is that which maintained satisfactory ventilation for at least 15 minutes

Reversal of postoperative respiratory depression, reversal of respiratory and CNS depression in neonate following maternal opioid use during labour section 15.1.7

Administration for *continuous intravenous infusion*, dilute to a concentration of up to 200 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%

¹ Naloxone (Non-proprietary) (PoM)

Injection, naloxone hydrochloride 20 micrograms/mL, net price 2-mL amp = £5.50; 400 micrograms/mL, net price 1-mL amp = £4.10; 1 mg/mL, 2-mL prefilled syringe = £16.50

¹ Minijet® Naloxone (UCB Pharma) (PoM)

Injection, naloxone hydrochloride 400 micrograms/mL, net price 1-mL disposable syringe = £20.40, 2-mL disposable syringe = £12.96, 5-mL disposable syringe = £20.40

Antidepressants

Tricyclic and related antidepressants Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Metabolic acidosis may complicate severe poisoning; delirium with confusion, agitation, and visual and auditory hallucinations, are common during recovery.

Assessment in hospital is strongly advised in case of poisoning by *tricyclic and related antidepressants* but symptomatic treatment can be given before transfer. Supportive measures to ensure a clear airway and adequate ventilation during transfer are mandatory. Intravenous lorazepam or diazepam (preferably in emulsion form) may be required to treat convulsions. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Although arrhythmias are worrying, some will respond to correction of hypoxia and acidosis. The use of anti-arrhythmic drugs is best avoided, but intravenous infusion of sodium bicarbonate can arrest arrhythmias or prevent them in those with an extended QRS duration. Diazepam given by mouth is usually adequate to sedate delirious children but large doses may be required.

Selective serotonin re-uptake inhibitors (SSRIs)

Symptoms of poisoning by selective serotonin re-uptake inhibitors include nausea, vomiting, agitation, tremor, nystagmus, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic instability; hyperthermia, rhabdomyolysis, renal failure, and coagulopathies may develop.

Management of SSRI poisoning is supportive. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Convulsions can be treated with lorazepam, diazepam, or buccal midazolam (see p. 24). Contact the National Poisons Information Service for the management of hyperthermia or the serotonin syndrome.

Antimalarials

Overdosage with quinine, chloroquine, or hydroxychloroquine is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features

1. (PoM) restriction does not apply where administration is for saving life in emergency

include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

Beta-blockers

Therapeutic overdosages with beta-blockers may cause lightheadedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. These complications are most likely in children with conduction system disorders or impaired myocardial function. Bradycardia is the most common arrhythmia caused by beta-blockers, but sotalol may induce ventricular tachyarrhythmias (sometimes of the torsade de pointes type). The effects of massive overdosage can vary from one beta-blocker to another; propranolol overdosage in particular may cause coma and convulsions.

Acute massive overdosage must be managed in hospital and expert advice should be obtained. Maintenance of a clear airway and adequate ventilation is mandatory. An intravenous injection of atropine is required to treat bradycardia (40 micrograms/kg, max. 3 mg). Cardio-genic shock unresponsive to atropine is probably best treated with an intravenous injection of glucagon (50–150 micrograms/kg, max. 10 mg) [unlicensed indication and dose] in glucose 5% (with precautions to protect the airway in case of vomiting) followed by an intravenous infusion of 50 micrograms/kg/hour. If glucagon is not available, intravenous isoprenaline (available from 'special-order' manufacturers or specialist importing companies, see p. 840) is an alternative. A cardiac pace-maker can be used to increase the heart rate.

Calcium-channel blockers

Features of calcium-channel blocker poisoning include nausea, vomiting, dizziness, agitation, confusion, and coma in severe poisoning. Metabolic acidosis and hyperglycaemia may occur. Verapamil and diltiazem have a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole. The dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

Activated charcoal should be considered if the child presents within 1 hour of overdosage with a calcium-channel blocker; repeated doses of activated charcoal are considered if a modified-release preparation is involved (although activated charcoal may be effective beyond 1 hour with modified-release preparations). In children with significant features of poisoning, calcium chloride or calcium gluconate (section 9.5.1.1) is given by injection; atropine is given to correct symptomatic bradycardia. In severe cases, an insulin and glucose infusion may be required in the management of hypotension and myocardial failure. For the management of hypotension, the choice of inotropic sympathomimetic depends on whether hypotension is secondary to vasodilatation or to myocardial depression—advice should be sought from the National Poisons Information Service (p. 23).

Hypnotics and anxiolytics

Benzodiazepines Benzodiazepines taken alone cause drowsiness, ataxia, dysarthria, nystagmus, and occasionally respiratory depression, and coma. They potentiate the effects of other central nervous system depressants taken concomitantly. Activated charcoal

can be given within 1 hour of ingesting a significant quantity of benzodiazepine, provided the child is awake and the airway is protected. Use of the benzodiazepine antagonist flumazenil [unlicensed indication] can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients. Flumazenil may prevent the need for ventilation, particularly in children with severe respiratory disorders; it should be used on expert advice and not as a diagnostic test in children with a reduced level of consciousness.

Iron salts

Iron poisoning in childhood is usually accidental. The symptoms are nausea, vomiting, abdominal pain, diarrhoea, haematemesis, and rectal bleeding. Hypotension and hepatocellular necrosis can occur later. Coma, shock and metabolic acidosis indicate severe poisoning. Advice should be sought from the National Poisons Information Service if a significant quantity of iron has been ingested within the previous hour.

Mortality is reduced by intensive and specific therapy with **desferrioxamine**, which chelates iron. The serum-iron concentration is measured as an emergency and intravenous desferrioxamine given to chelate absorbed iron in excess of the expected iron binding capacity. In **severe toxicity** intravenous desferrioxamine should be given *immediately* without waiting for the result of the serum-iron measurement.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

DESFERIOXAMINE MESILATE (Deferoxamine Mesilate)

Cautions section 9.1.3

Renal impairment section 9.1.3

Pregnancy section 9.1.3

Breast-feeding section 9.1.3

Side-effects section 9.1.3

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Iron poisoning

- By continuous intravenous infusion

Neonate up to 15 mg/kg/hour, reduced after 4–6 hours; max. 80 mg/kg in 24 hours (in severe cases, higher doses on advice from the National Poisons Information Service)

Child 1 month–18 years up to 15 mg/kg/hour, reduced after 4–6 hours; max. 80 mg/kg in 24 hours (in severe cases, higher doses on advice from the National Poisons Information Service)

Chronic iron overload section 9.1.3

Preparations

Section 9.1.3

Lithium

Lithium intoxication can occur as a complication of long-term therapy and is caused by reduced excretion of the drug because of a variety of factors including dehydration, deterioration of renal function, infections,

and co-administration of diuretics or NSAIDs (or other drugs that interact). Acute deliberate overdoses may also occur with delayed onset of symptoms (12 hours or more) due to slow entry of lithium into the tissues and continuing absorption from modified-release formulations.

The early clinical features are non-specific and may include apathy and restlessness which could be confused with mental changes due to the child's depressive illness. Vomiting, diarrhoea, ataxia, weakness, dysarthria, muscle twitching, and tremor may follow. Severe poisoning is associated with convulsions, coma, renal failure, electrolyte imbalance, dehydration, and hypotension.

Therapeutic serum-lithium concentrations are within the range of 0.4–1 mmol/litre; concentrations in excess of 2 mmol/litre are usually associated with serious toxicity and such cases may need treatment with haemodialysis if neurological symptoms or renal failure are present. In acute overdosage, much higher serum-lithium concentrations may be present without features of toxicity and all that is usually necessary is to take measures to increase urine output (e.g. by increasing fluid intake, but avoiding diuretics). Otherwise, treatment is supportive with special regard to electrolyte balance, renal function, and control of convulsions. Whole-bowel irrigation should be considered for significant ingestion, but advice should be sought from the National Poisons Information Service (p. 23).

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

Phenothiazines and related drugs

Phenothiazines cause less depression of consciousness and respiration than other sedatives. Hypotension, hypothermia, sinus tachycardia, and arrhythmias may complicate poisoning. Dystonic reactions can occur with therapeutic doses (particularly with prochlorperazine and trifluoperazine), and convulsions may occur in severe cases. Arrhythmias may respond to correction of hypoxia, acidosis, and other biochemical abnormalities, but specialist advice should be sought if arrhythmias result from a prolonged QT interval; the use of some anti-arrhythmic drugs can worsen such arrhythmias. Dystonic reactions are rapidly abolished by injection of drugs such as procyclidine (section 4.9.2) or diazepam (section 4.8.2, emulsion preferred).

Second-generation antipsychotic drugs

Features of poisoning by second-generation antipsychotic drugs (section 4.2.1) include drowsiness, convulsions, extrapyramidal symptoms, hypotension, and ECG abnormalities (including prolongation of the QT interval). Management is supportive. Activated charcoal can be given within 1 hour of ingesting a significant quantity of a second-generation antipsychotic drug.

Stimulants

Amfetamines Amfetamines cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. The early stages can be controlled

by diazepam or lorazepam; advice should be sought from the National Poisons Information Service (p. 23) on the management of hypertension. Later, tepid sponging, anticonvulsants, and artificial respiration may be needed.

Cocaine Cocaine stimulates the central nervous system, causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hyperthermia, hypertonica, and hyperreflexia; cardiac effects include chest pain, myocardial infarction, and arrhythmias.

Initial treatment of cocaine poisoning involves cooling measures for hyperthermia (see p. 24); agitation, hypertension, and cardiac effects require specific treatment and expert advice should be sought.

Ecstasy Ecstasy (methylenedioxymethamphetamine, MDMA) may cause severe reactions, even at doses that were previously tolerated. The most serious effects are delirium, coma, convulsions, ventricular arrhythmias, hyperthermia, rhabdomyolysis, acute renal failure, acute hepatitis, disseminated intravascular coagulation, adult respiratory distress syndrome, hyperreflexia, hypotension and intracerebral haemorrhage; hyponatraemia has also been associated with ecstasy use and syndrome of inappropriate antidiuretic hormone secretion (SIADH) can occur.

Treatment of methylenedioxymethamphetamine poisoning is supportive, with diazepam to control persistent convulsions and close monitoring including ECG. For the management of agitation, seek specialist advice. Self-induced water intoxication should be considered in patients with ecstasy poisoning.

'Liquid ecstasy' is a term used for sodium oxybate (gamma-hydroxybutyrate, GHB), which is a sedative.

Theophylline

Theophylline and related drugs are often prescribed as modified-release formulations and toxicity can therefore be delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

Repeated doses of activated charcoal can be used to eliminate theophylline even if more than 1 hour has elapsed after ingestion and especially if a modified-release preparation has been taken (see also under Active Elimination Techniques). Ondansetron (section 4.6) may be effective for severe vomiting that is resistant to other antiemetics. Hypokalaemia is corrected by intravenous infusion of potassium chloride (section 9.2.2.1) in 0.9% sodium chloride and may be so severe as to require high doses under ECG monitoring. Convulsions should be controlled by intravenous administration of lorazepam or diazepam (see Convulsions, p. 24). For the management of agitation associated with theophylline overdosage, seek specialist advice.

Provided the child does **not** suffer from asthma, a short-acting beta-blocker (section 2.4) can be administered intravenously to reverse severe tachycardia, hypokalaemia, and hyperglycaemia.

Other poisons

Consult either the National Poisons Information Service day and night or TOXBASE, see p. 23.

Cyanides

Oxygen should be administered to children with cyanide poisoning. The choice of antidote depends on the severity of poisoning, certainty of diagnosis, and the cause. **Dicobalt edetate** is the antidote of choice when there is a strong clinical suspicion of severe cyanide poisoning. Dicobalt edetate itself is toxic, associated with anaphylactoid reactions, and is potentially fatal if administered in the absence of cyanide poisoning. A regimen of **sodium nitrite** followed by **sodium thiosulfate** is an alternative if dicobalt edetate is not available.

Hydroxocobalamin (*Cyanokit*®)—no other preparation of hydroxocobalamin is suitable) can be considered for use in victims of smoke inhalation who show signs of significant cyanide poisoning.

DICOBALT EDETATE

Cautions owing to toxicity to be used only for definite cyanide poisoning when patient tending to lose, or has lost, consciousness; **not** to be used as a precautionary measure

Side-effects hypotension, tachycardia, and vomiting; anaphylactoid reactions including facial and laryngeal oedema and cardiac abnormalities

Indications and dose

Severe poisoning with cyanides

- By intravenous injection

Consult the National Poisons Information Service

¹Dicobalt Edetate (Non-proprietary) (PoM)

Injection, dicobalt edetate 15 mg/mL, net price 20-mL (300-mg) amp = £16.99

HYDROXOCOBALAMIN

Side-effects gastro-intestinal disturbances, transient hypertension, peripheral oedema, dyspnoea, throat disorders, hot flush, dizziness, headache, restlessness, memory impairment, red coloration of urine, lymphocytopenia, eye disorders, pustular rashes, pruritus, reversible red coloration of skin and mucous membranes

Indications and dose

Poisoning with cyanides see notes above

- By intravenous infusion

Child body-weight 5 kg and over 70 mg/kg (max. 5 g) over 15 minutes; a second dose of 70 mg/kg (max. 5 g) can be given over 15 minutes–2 hours depending on severity of poisoning and patient stability

Administration for *intravenous infusion*, reconstitute 5-g vial with 200 mL Sodium Chloride 0.9%; gently invert vial for at least 1 minute to mix (do not shake)

Cyanokit® (Swedish Orphan) (PoM)

Intravenous infusion, powder for reconstitution, hydroxocobalamin, net price 5-g vial = £772.00

Note Deep red colour of hydroxocobalamin may interfere with laboratory tests (see Side-effects, above) and haemodialysis

1. (PoM) restriction does not apply where administration is for saving life in emergency

SODIUM NITRITE

Side-effects flushing and headache due to vasodilatation

Indications and dose

Poisoning with cyanides (used in conjunction with sodium thiosulfate)

See under preparation

¹Sodium Nitrite (PoM)

Injection, sodium nitrite 3% (30 mg/mL) in water for injections

Dose

- By intravenous injection over 5–20 minutes

Child 1 month–18 years 4–10 mg/kg max. 300 mg (0.13–0.33 mL/kg, max. 10 mL, of 3% solution) followed by sodium thiosulfate injection 400 mg/kg, max. 12.5 g (0.8 mL/kg, max. 25 mL, of 50% solution) over 10 minutes

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

SODIUM THIOSULFATE

Indications and dose

Poisoning with cyanides (used in conjunction with sodium nitrite)

See above under Sodium Nitrite

¹Sodium Thiosulfate (PoM)

Injection, sodium thiosulfate 50% (500 mg/mL) in water for injections

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Ethylene glycol and methanol

Fomepizole (available from 'special-order' manufacturers or specialist importing companies, see p. 840) is the treatment of choice for ethylene glycol and methanol (methyl alcohol) poisoning. If necessary, **ethanol** (by mouth or by intravenous infusion) can be used, but with caution. Advice on the treatment of ethylene glycol and methanol poisoning should be obtained from the National Poisons Information Service. It is important to start antidote treatment promptly in cases of suspected poisoning with these agents.

Heavy metals

Heavy metal antidotes include succimer (DMSA) [unlicensed], unithiol (DMPS) [unlicensed], sodium calcium edetate [unlicensed], and dimercaprol. Dimercaprol in the management of heavy metal poisoning has been superseded by other chelating agents. In all cases of heavy metal poisoning, the advice of the National Poisons Information Service should be sought.

Noxious gases

Carbon monoxide Carbon monoxide poisoning is usually due to inhalation of smoke, car exhaust, or fumes caused by blocked flues or incomplete combustion of fuel gases in confined spaces.

Immediate treatment of carbon monoxide poisoning is essential. The child should be moved to fresh air, the airway cleared, and high-flow **oxygen** 100% administered as soon as available. Artificial respiration should be given as necessary and continued until adequate spontaneous breathing starts, or stopped only after persistent and efficient treatment of cardiac arrest has failed. The child should be admitted to hospital because

complications may arise after a delay of hours or days. Cerebral oedema may occur in severe poisoning and is treated with an intravenous infusion of mannitol (section 2.2.5). Referral for hyperbaric oxygen treatment should be discussed with the National Poisons Information Service if the patient is pregnant or in cases of severe poisoning such as if the child is or has been unconscious, or has psychiatric or neurological features other than a headache or has myocardial ischaemia or an arrhythmia, or has a blood carboxyhaemoglobin concentration of more than 20%.

Sulfur dioxide, chlorine, phosgene, ammonia

All of these gases can cause upper respiratory tract and conjunctival irritation. Pulmonary oedema, with severe breathlessness and cyanosis may develop suddenly up to 36 hours after exposure. Death may occur. Children are kept under observation and those who develop pulmonary oedema are given oxygen. Assisted ventilation may be necessary in the most serious cases.

CS Spray

CS spray, which is used for riot control, irritates the eyes (hence 'tear gas') and the respiratory tract; symptoms normally settle spontaneously within 15 minutes. If symptoms persist, the patient should be removed to a well-ventilated area, and the exposed skin washed with soap and water after removal of contaminated clothing. Contact lenses should be removed and rigid ones washed (soft ones should be discarded). Eye symptoms should be treated by irrigating the eyes with physiological saline (or water if saline is not available) and advice sought from an ophthalmologist. Patients with features of severe poisoning, particularly respiratory complications, should be admitted to hospital for symptomatic treatment.

Nerve agents

Treatment of nerve agent poisoning is similar to organophosphorus insecticide poisoning (see below), but advice must be sought from the National Poisons Information Service. The risk of cross-contamination is significant; adequate decontamination and protective clothing for healthcare personnel are essential. In emergencies involving the release of nerve agents, kits ('NAAS pods') containing **pralidoxime** can be obtained through the Ambulance Service from the National Blood Service (or the Welsh Blood Service in South Wales or designated hospital pharmacies in Northern Ireland and Scotland—see TOXBASE for list of designated centres).

Pesticides

Organophosphorus insecticides Organophosphorus insecticides are usually supplied as powders or dissolved in organic solvents. All are absorbed through the bronchi and intact skin as well as through the gut and inhibit cholinesterase activity, thereby prolonging and intensifying the effects of acetylcholine. Toxicity between different compounds varies considerably, and onset may be delayed after skin exposure.

Anxiety, restlessness, dizziness, headache, miosis, nausea, hypersalivation, vomiting, abdominal colic, diarrhoea, bradycardia, and sweating are common features of organophosphorus poisoning. Muscle weakness and fasciculation may develop and progress to generalised flaccid paralysis, including the ocular and respiratory muscles. Convulsions, coma, pulmonary oedema with copious bronchial secretions, hypoxia, and arrhythmias occur in severe cases. Hyperglycaemia and glycosuria without ketonuria may also be present.

Further absorption of the organophosphorus insecticide should be prevented by moving the child to fresh air, removing soiled clothing, and washing contaminated skin. In severe poisoning it is vital to ensure a clear airway, frequent removal of bronchial secretions, and adequate ventilation and oxygenation; gastric lavage may be considered provided that the airway is protected. **Atropine** will reverse the muscarinic effects of acetylcholine and is given by intravenous injection in a dose of 20 micrograms/kg (max. 2 mg) as atropine sulfate every 5 to 10 minutes (according to the severity of poisoning) until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished.

Pralidoxime chloride, a cholinesterase reactivator, is used as an adjunct to atropine in moderate or severe poisoning. It improves muscle tone within 30 minutes of administration. Pralidoxime chloride is continued until the patient has not required atropine for 12 hours. Pralidoxime chloride can be obtained from designated centres, the names of which are held by the National Poisons Information Service (see p. 23).

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

PRALIDOXIME CHLORIDE

Cautions myasthenia gravis

Contra-indications poisoning with carbamates or organophosphorus compounds without anticholinesterase activity

Renal impairment use with caution

Side-effects drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation, and muscular weakness

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Adjunct to atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent

- By intravenous infusion over 20 minutes

Child under 18 years initially 30 mg/kg, followed by 8 mg/kg/hour; usual max. 12 g in 24 hours

Note The loading dose may be administered by intravenous injection (diluted to a concentration of 50 mg/mL with water for injections) over at least 5 minutes if pulmonary oedema is present or if it is not practical to administer an intravenous infusion; pralidoxime chloride doses may differ from those in product literature

Administration for intravenous infusion, reconstitute each vial with 20 mL Water for Injections, then dilute to a concentration of 10–20 mg/mL with Sodium Chloride 0.9%

¹ Pralidoxime chloride ^(PoM)

Injection, powder for reconstitution, pralidoxime chloride 1 g/vial

Available as **Protopam**® (from designated centres for organophosphorus insecticide poisoning or from the National Blood Service (or Welsh Ambulance Services for Mid West and South East Wales)—see TOXBASE for list of designated centres)

1. ^(PoM) restriction does not apply where administration is for saving life in emergency

Snake bites and animal stings

Snake bites Envenoming from snake bite is uncommon in the UK. Many exotic snakes are kept, some illegally, but the only indigenous venomous snake is the adder (*Vipera berus*). The bite may cause local and systemic effects. Local effects include pain, swelling, bruising, and tender enlargement of regional lymph nodes. Systemic effects include early anaphylactic symptoms (transient hypotension with syncope, angioedema, urticaria, abdominal colic, diarrhoea, and vomiting), with later persistent or recurrent hypotension, ECG abnormalities, spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome, and acute renal failure. Fatal envenoming is rare but the potential for severe envenoming must not be underestimated.

Early anaphylactic symptoms should be treated with **adrenaline (epinephrine)** (section 3.4.3). Indications for antivenom treatment include *systemic envenoming*, especially hypotension (see above), ECG abnormalities, vomiting, haemostatic abnormalities, and marked local envenoming such that after bites on the hand or foot, swelling extends beyond the wrist or ankle within 4 hours of the bite. The contents of one vial (10 mL) of **European viper venom antiserum** (to order, email immform@dh.gsi.gov.uk) is given by *intravenous injection* over 10–15 minutes or by *intravenous infusion* over 30 minutes after diluting in sodium chloride 0.9% (use 5 mL diluent/kg body-weight). The **same dose** should be used for **adults** and **children**. The dose can be repeated after 1–2 hours if symptoms of *systemic envenoming* persist. However, for those children who present with clinical features of *severe envenoming* (e.g. shock, ECG abnormalities, or local swelling that has advanced from the foot to above the knee or from the hand to above the elbow within 2 hours of the bite), an initial dose of 2 vials (20 mL) of the antiserum is recommended; if symptoms of *systemic envenoming* persist contact the National Poisons Information Service. Adrenaline (epinephrine) injection must be immediately to hand for treatment of anaphylactic reactions to the antivenom (for the management of anaphylaxis see section 3.4.3).

Antivenom is available for bites by certain foreign snakes and spiders, stings by scorpions and fish. For information on identification, management, and for supply in an emergency, telephone the National Poisons Information Service. Whenever possible the TOXBASE entry should be read, and relevant information collected, before telephoning the National Poisons Information Service (see p. 23).

Insect stings Stings from ants, wasps, hornets, and bees cause local pain and swelling but seldom cause severe direct toxicity unless many stings are inflicted at the same time. If the sting is in the mouth or on the tongue local swelling may threaten the upper airway. The stings from these insects are usually treated by cleaning the area with a topical antiseptic. Bee stings should be removed as quickly as possible. Anaphylactic reactions require immediate treatment with intramuscular **adrenaline (epinephrine)**; self-administered (or administered by a carer) intramuscular adrenaline (e.g. *EpiPen*®) is the best first-aid treatment for children with severe hypersensitivity. An inhaled bronchodilator should be used for asthmatic reactions. For the management of anaphylaxis, see section 3.4.3. A short course of an **oral antihistamine** or a **topical corticosteroid** may

help to reduce inflammation and relieve itching. A vaccine containing extracts of bee and wasp venom can be used to reduce the risk of severe anaphylaxis and systemic reactions in children with systemic hypersensitivity to bee or wasp stings (section 3.4.2).

Marine stings The severe pain of weeverfish (*Trachinus vipera*) and Portuguese man-o'-war stings can be relieved by immersing the stung area immediately in uncomfortably hot, but not scalding, water (not more than 45°C). Children stung by jellyfish and Portuguese man-o'-war around the UK coast should be removed from the sea as soon as possible. Adherent tentacles should be lifted off carefully (wearing gloves or using tweezers) or washed off with seawater. Alcoholic solutions, including suntan lotions, should **not** be applied because they can cause further discharge of stinging hairs. Ice packs can be used to reduce pain.

1 Gastro-intestinal system

1.1 Dyspepsia and gastro-oesophageal reflux disease	34	1.9 Drugs affecting intestinal secretions	68
1.1.1 Antacids and simeticone	35	1.9.1 Drugs affecting biliary composition and flow	68
1.1.2 Compound alginate preparations	36	1.9.2 Bile acid sequestrants	69
1.2 Antispasmodics and other drugs altering gut motility	37	1.9.3 Aprotinin	69
1.3 Antisecretory drugs and mucosal protectants	40	1.9.4 Pancreatin	69
1.3.1 H ₂ -receptor antagonists	41	<div> <p>This chapter includes advice on the drug management of the following:</p> <ul style="list-style-type: none"> <i>Clostridium difficile</i> infection, p. 48 constipation, p. 56 Crohn's disease, p. 47 food allergy, p. 56 <i>Helicobacter pylori</i> infection, p. 40 irritable bowel syndrome, p. 48 malabsorption syndromes, p. 49 NSAID-associated ulcers, p. 41 ulcerative colitis, p. 47 </div>	
1.3.2 Selective antimuscarinics	42		
1.3.3 Chelates and complexes	42		
1.3.4 Prostaglandin analogues	43		
1.3.5 Proton pump inhibitors	43		
1.4 Acute diarrhoea	45		
1.4.1 Adsorbents and bulk-forming drugs	45		
1.4.2 Antimotility drugs	45		
1.4.3 Enkephalinase inhibitors	47		
1.5 Chronic bowel disorders	47		
1.5.1 Aminosaliclates	49	<div> 1.1 Dyspepsia and gastro-oesophageal reflux disease </div>	
1.5.2 Corticosteroids	52		
1.5.3 Drugs affecting the immune response	53	1.1.1 Antacids and simeticone	
1.5.4 Food allergy	56	1.1.2 Compound alginate preparations	
1.6 Laxatives	56	<div> Dyspepsia <p>Dyspepsia covers upper abdominal pain, fullness, early satiety, bloating, and nausea. It can occur with gastric and duodenal ulceration (section 1.3), gastro-oesophageal reflux disease, gastritis, and upper gastro-intestinal motility disorders, but most commonly it is of uncertain origin.</p> <p>Children with dyspepsia should be advised about lifestyle changes (see Gastro-oesophageal reflux disease, below). Some medications may cause dyspepsia—these should be stopped, if possible.</p> <p>A compound alginate preparation (section 1.1.2) may provide relief from dyspepsia; persistent dyspepsia requires investigation. Treatment with a H₂-receptor antagonist (section 1.3.1) or a proton pump inhibitor (section 1.3.5) should be initiated only on the advice of a hospital specialist.</p> <p><i>Helicobacter pylori</i> may be present in children with dyspepsia. <i>H. pylori</i> eradication therapy (section 1.3) should be considered for persistent dyspepsia if it is ulcer-like. However, most children with functional (investigated, non-ulcer) dyspepsia do not benefit symptomatically from <i>H. pylori</i> eradication.</p> </div>	
1.6.1 Bulk-forming laxatives	57		
1.6.2 Stimulant laxatives	58		
1.6.3 Faecal softeners	60		
1.6.4 Osmotic laxatives	61		
1.6.5 Bowel cleansing preparations	63		
1.6.6 Peripheral opioid-receptor antagonists	65		
1.6.7 Other drugs used in constipation	65		
1.7 Local preparations for anal and rectal disorders	65		
1.7.1 Soothing anal and rectal preparations	65	<div> Gastro-oesophageal reflux disease <p>Gastro-oesophageal reflux disease includes non-erosive gastro-oesophageal reflux and erosive oesophagitis. Uncomplicated gastro-oesophageal reflux is common in infancy and most symptoms, such as intermittent</p> </div>	
1.7.2 Compound anal and rectal preparations with corticosteroids	65		
1.7.3 Rectal sclerosants	67		
1.7.4 Management of anal fissures	67		
1.8 Stoma and enteral feeding tubes	67		

vomiting or repeated, effortless regurgitation, resolve without treatment between 12 and 18 months of age. Older children with gastro-oesophageal reflux disease may have heartburn, acid regurgitation and dysphagia. Oesophageal inflammation (oesophagitis), ulceration or stricture formation may develop in early childhood; gastro-oesophageal reflux disease may also be associated with chronic respiratory disorders including asthma.

Parents and carers of *neonates* and *infants* should be reassured that most symptoms of uncomplicated gastro-oesophageal reflux resolve without treatment. An increase in the frequency and a decrease in the volume of feeds may reduce symptoms. A feed thickener or pre-thickened formula feed (Appendix 2) can be used on the advice of a dietician. If necessary, a suitable alginate-containing preparation (section 1.1.2) can be used instead of thickened feeds.

Older children should be advised about life-style changes such as weight reduction if overweight, and the avoidance of alcohol and smoking. An alginate-containing antacid (section 1.1.2) can be used to relieve symptoms.

Children who do not respond to these measures or who have problems such as respiratory disorders or suspected oesophagitis need to be referred to hospital. On the advice of a paediatrician, a **histamine H₂-receptor antagonist** (section 1.3.1) can be used to relieve symptoms of gastro-oesophageal reflux disease, promote mucosal healing and permit reduction in antacid consumption. A **proton pump inhibitor** (section 1.3.5) can be used for the treatment of moderate, non-erosive oesophagitis that is unresponsive to an H₂-receptor antagonist. Endoscopically confirmed *erosive*, *ulcerative*, or *stricturing* disease in children is usually treated with a proton pump inhibitor. Reassessment is necessary if symptoms persist despite 4–6 weeks of treatment; long-term use of an H₂-receptor antagonist or proton pump inhibitor should not be undertaken without full assessment of the underlying condition. For endoscopically confirmed *erosive*, *ulcerative*, or *stricturing* disease, the proton pump inhibitor usually needs to be maintained at the minimum effective dose.

Motility stimulants (section 1.2), such as erythromycin may improve gastro-oesophageal sphincter contraction and accelerate gastric emptying. Evidence for the long-term efficacy of motility stimulants in the management of gastro-oesophageal reflux in children is unconvincing.

For advice on specialised formula feeds, see section 9.4.2.

Pregnancy If dietary and lifestyle changes (see notes above) fail to control gastro-oesophageal reflux disease in pregnancy, an antacid (section 1.1.1) or an alginate (section 1.1.2) can be used. If this is ineffective, ranitidine (section 1.3.1) can be tried. Omeprazole (section 1.3.5) is reserved for women with severe or complicated reflux disease.

1.1.1 Antacids and simeticone

Antacids (usually containing aluminium or magnesium compounds) can be used for short-term relief of intermittent symptoms of *ulcer dyspepsia* and *non-erosive gastro-oesophageal reflux* (see section 1.1) in children; they are also used in functional (non-ulcer) dyspepsia, but the evidence of benefit is uncertain.

Aluminium- and magnesium-containing antacids, being relatively insoluble in water, are long-acting if

retained in the stomach. Magnesium-containing antacids tend to be laxative whereas aluminium-containing antacids may be constipating; antacids containing both magnesium and aluminium may reduce these colonic side-effects. Aluminium-containing antacids should not be used in children with renal impairment, or in neonates and infants because accumulation may lead to increased plasma-aluminium concentrations.

Complexes such as **hydrotalcite** confer no special advantage.

Calcium-containing antacids can induce rebound acid secretion; with modest doses the clinical significance of this is doubtful, but prolonged high doses also cause hypercalcaemia and alkalosis.

Simeticone (activated dimeticone) is used to treat infantile colic, but the evidence of benefit is uncertain. Simeticone is added to an antacid as an antifoaming agent to relieve flatulence; such preparations may also be useful for the relief of hiccup in palliative care (see Prescribing in Palliative Care, p. 18).

Alginates act as mucosal protectants in gastro-oesophageal reflux disease (section 1.1.2). The amount of additional ingredient or antacid in individual preparations varies widely, as does their sodium content, so that preparations may not be freely interchangeable.

Hepatic impairment In children with fluid retention, avoid antacids containing large amounts of sodium. Avoid antacids that cause constipation because this can precipitate coma. Avoid antacids containing magnesium salts in hepatic coma if there is a risk of renal failure.

Renal impairment In children with fluid retention, avoid antacids containing large amounts of sodium. There is a risk of accumulation and aluminium toxicity with antacids containing aluminium salts. Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics). Antacids containing magnesium salts should be avoided or used at a reduced dose because there is an increased risk of toxicity.

Interactions Antacids should preferably not be taken at the same time as other drugs since they may impair absorption. Antacids may also damage enteric coatings designed to prevent dissolution in the stomach. See also **Appendix 1** (antacids, calcium salts).

Low Na⁺

The words 'low Na⁺' added after some preparations indicate a sodium content of less than 1 mmol per tablet or 10-mL dose.

Aluminium- and magnesium-containing antacids

ALUMINIUM HYDROXIDE

Cautions see notes above; **interactions:** Appendix 1 (antacids)

Contra-indications hypophosphataemia; neonates and infants

Hepatic impairment see notes above

Renal impairment see notes above

Side-effects see notes above

Indications and dose

Dyspepsia for dose see preparations

Hyperphosphataemia section 9.5.2.2

Co-magaldrox

Co-magaldrox is a mixture of aluminium hydroxide and magnesium hydroxide; the proportions are expressed in the form x/y where x and y are the strengths in milligrams per unit dose of magnesium hydroxide and aluminium hydroxide respectively

Maalox® (Sanofi-Aventis)

Suspension, sugar-free, co-magaldrox 195/220 (magnesium hydroxide 195 mg, dried aluminium hydroxide 220 mg/5 mL (low Na⁺)). Net price 500 mL = £3.35

Dose

- By mouth

Child 14–18 years 10–20 mL 20–60 minutes after meals and at bedtime, or when required

Mucogel® (Chemidex)

Suspension, sugar-free, co-magaldrox 195/220 (magnesium hydroxide 195 mg, dried aluminium hydroxide 220 mg/5 mL (low Na⁺)). Net price 500 mL = £2.99

Dose

- By mouth

Child 12–18 years 10–20 mL 3 times daily, 20–60 minutes after meals and at bedtime, or when required

MAGNESIUM TRISILICATE

Cautions heart failure, hypertension; metabolic or respiratory alkalosis, hypermagnesaemia; **interactions:** Appendix 1 (antacids)

Contra-indications severe renal failure; hypophosphataemia

Hepatic impairment see notes above

Renal impairment see notes above; magnesium trisilicate mixture has a high sodium content

Side-effects see notes above; silica-based renal stones reported on long-term treatment

Indications and dose

Dyspepsia for dose see under preparation

Magnesium Trisilicate Mixture, BP

(Magnesium Trisilicate Oral Suspension)

Oral suspension, 5% each of magnesium trisilicate, light magnesium carbonate, and sodium bicarbonate in a suitable vehicle with a peppermint flavour. Contains about 6 mmol Na⁺/10 mL

Dose

- By mouth

Child 5–12 years 5–10 mL with water 3 times daily or as required

Child 12–18 years 10–20 mL with water 3 times daily or as required

Aluminium-magnesium complexes**HYDROTALCITE**

Aluminium magnesium carbonate hydroxide hydrate

Cautions see notes above; **interactions:** Appendix 1 (antacids)

Hepatic impairment see notes above

Renal impairment see notes above

Side-effects see notes above

Indications and dose

Dyspepsia for dose see under preparation

With simeticone**Altacite Plus®**

see below

Antacid preparations containing simeticone**Altacite Plus®** (Peckforton)

Suspension, sugar-free, co-simacite 125/500 (simeticone 125 mg, hydrotalcite 500 mg)/5 mL (low Na⁺). Net price 500 mL = £3.20

Dose

- By mouth

Child 8–12 years 5 mL 4 times daily (between meals and at bedtime) when required

Child 12–18 years 10 mL 4 times daily (between meals and at bedtime) when required

Maalox Plus® (Sanofi-Aventis)

Suspension, sugar-free, dried aluminium hydroxide 220 mg, simeticone 25 mg, magnesium hydroxide 195 mg/5 mL (low Na⁺). Net price 500 mL = £3.90

Dose

- By mouth

Child 2–5 years 5 mL 3 times daily

Child 5–12 years 5–10 mL 3–4 times daily

Child 12–18 years 5–10 mL 4 times daily (after meals and at bedtime) or when required

Simeticone alone**SIMETICONE**

Activated dimeticone

Indications and dose

Colic or wind pain for dose see under individual preparations

Dentinox® (DDD) 

Colic drops (= emulsion), simeticone 21 mg/2.5 mL dose. Net price 100 mL = £1.73

Dose

- By mouth

Neonate 2.5 mL with or after each feed (max. 6 doses in 24 hours); may be added to bottle feed

Child 1 month–2 years 2.5 mL with or after each feed (max. 6 doses in 24 hours); may be added to bottle feed

Note The brand name *Dentinox®* is also used for other preparations including teething gel

Infacol® (Forest) 

Liquid, sugar-free, simeticone 40 mg/mL (low Na⁺). Net price 50 mL = £2.71. Counselling, use of dropper

Dose

- By mouth

Neonate 0.5–1 mL before feeds

Child 1 month–2 years 0.5–1 mL before feeds

1.1.2 Compound alginate preparations

Alginate taken in combination with an antacid increases the viscosity of stomach contents and can protect the oesophageal mucosa from acid reflux. Some alginate-containing preparations form a viscous gel ('raft') that

floats on the surface of the stomach contents, thereby reducing symptoms of reflux. Alginate-containing preparations are used in the management of mild symptoms of dyspepsia and gastro-oesophageal reflux disease (see section 1.1). Antacids may damage enteric coatings designed to prevent dissolution in the stomach. For **interactions**, see Appendix 1 (antacids, calcium salts).

Preparations containing aluminium should not be used in children with renal impairment, or in neonates and infants.

Alginate raft-forming oral suspensions

The following preparations contain sodium alginate, sodium bicarbonate, and calcium carbonate in a suitable flavoured vehicle, and conform to the specification for Alginate Raft-forming Oral Suspension, BP.

Acidex® (Pinewood)

Liquid, sugar-free, sodium alginate 250 mg, sodium bicarbonate 133.5 mg, calcium carbonate 80 mg/5 mL. Contains about 3 mmol Na⁺/5 mL, net price 500 mL (aniseed- or peppermint-flavour) = £2.50

Dose

• By mouth

Child 6–12 years 5–10 mL after meals and at bedtime

Child 12–18 years 10–20 mL after meals and at bedtime

Gaviscon® (Reckitt Benckiser)

Suspension, sugar-free, aniseed- or peppermint flavour, sodium alginate 250 mg, sodium bicarbonate 133.5 mg, calcium carbonate 80 mg/5 mL. Contains 3.1 mmol Na⁺/5 mL. Net price 300 mL = £4.20, 600 mL = £6.89

Dose

• By mouth

Child 6–12 years 5–10 mL after meals and at bedtime

Child 12–18 years 10–20 mL after meals and at bedtime

Peptac® (TEVA UK)

Suspension, sugar-free, sodium bicarbonate 133.5 mg, sodium alginate 250 mg, calcium carbonate 80 mg/5 mL. Contains 3.1 mmol Na⁺/5 mL. Net price 500 mL (aniseed- or peppermint-flavoured) = £1.95

Dose

• By mouth

Child 6–12 years 5–10 mL after meals and at bedtime

Child 12–18 years 10–20 mL after meals and at bedtime

Other compound alginate preparations

Gastrocote® (Actavis)

Tablets, alginic acid 200 mg, dried aluminium hydroxide 80 mg, magnesium trisilicate 40 mg, sodium bicarbonate 70 mg. Contains about 1 mmol Na⁺/tablet. Net price 100-tab pack = £3.51

Cautions diabetes mellitus (high sugar content)

Dose

• By mouth

Child 6–18 years 1–2 tablets chewed 4 times daily (after meals and at bedtime)

Liquid, sugar-free, peach-coloured, dried aluminium hydroxide 80 mg, magnesium trisilicate 40 mg, sodium alginate 220 mg, sodium bicarbonate 70 mg/5 mL. Contains 2.13 mmol Na⁺/5 mL. Net price 500 mL = £2.67

Dose

• By mouth

Child 6–12 years 5–10 mL 4 times daily (after meals and at bedtime)

Child 12–18 years 5–15 mL 4 times daily (after meals and at bedtime)

Gaviscon® Advance (Reckitt Benckiser)

Chewable tablets, sugar-free, sodium alginate 500 mg, potassium bicarbonate 100 mg. Contains 2.25 mmol Na⁺, 1 mmol K⁺/tablet. Net price 60-tab pack (peppermint-flavour) = £3.07

Excipients include aspartame (section 9.4.1)

Dose

• By mouth

Child 6–12 years 1 tablet to be chewed after meals and at bedtime (under medical advice only)

Child 12–18 years 1–2 tablets to be chewed after meals and at bedtime

Suspension, sugar-free, aniseed- or peppermint-flavour, sodium alginate 500 mg, potassium bicarbonate 100 mg/5 mL. Contains 2.3 mmol Na⁺, 1 mmol K⁺/5 mL, net price 250 mL = £2.61, 500 mL = £5.21

Dose

• By mouth

Child 2–12 years 2.5–5 mL after meals and at bedtime (under medical advice only)

Child 12–18 years 5–10 mL after meals and at bedtime

Gaviscon® Infant (Reckitt Benckiser)

Oral powder, sugar-free, sodium alginate 225 mg, magnesium alginate 87.5 mg, with colloidal silica and mannitol/dose. Contains 0.92 mmol Na⁺/dose. Net price 30 doses = £3.69

Dose

• By mouth

Neonate body-weight under 4.5 kg 1 'dose' mixed with feeds (or water, for breast-fed infants) when required (max. 6 times in 24 hours)

Neonate body-weight over 4.5 kg 2 'doses' mixed with feeds (or water, for breast-fed infants) when required (max. 6 times in 24 hours)

Child 1 month–2 years

Body-weight under 4.5 kg dose as for neonate

Body-weight over 4.5 kg 2 'doses' mixed with feeds (or water, for breast-fed infants) when required (max. 6 times in 24 hours)

Note Not to be used in preterm neonates, or where excessive water loss likely (e.g. fever, diarrhoea, vomiting, high room temperature), or if intestinal obstruction. Not to be used with other preparations containing thickening agents

Safe Practice

Each half of the dual sachet is identified as 'one dose'. To avoid errors prescribe with directions in terms of 'dose'

1.2 Antispasmodics and other drugs altering gut motility

Drugs in this section include antimuscarinic compounds and drugs believed to be direct relaxants of intestinal smooth muscle. The smooth muscle relaxant properties

of antimuscarinic and other antispasmodic drugs may be useful in *irritable bowel syndrome*.

Antimuscarinics

Antimuscarinics (formerly termed 'anticholinergics') reduce intestinal motility. They are occasionally used for the management of *irritable bowel syndrome* but the evidence of their value has not been established and response varies. Other indications for antimuscarinic drugs include asthma and airways disease (section 3.1.2), motion sickness (section 4.6), urinary frequency and enuresis (section 7.4.2), mydriasis and cycloplegia (section 11.5), premedication (section 15.1.3), palliative care (p. 18), and as an antidote to organophosphorus poisoning (p. 32).

Antimuscarinics that are used for gastro-intestinal smooth muscle spasm include the tertiary amine **dicycloverine hydrochloride** and the quaternary ammonium compounds **propantheline bromide** and **hyoscine butylbromide**. The quaternary ammonium compounds are less lipid soluble than atropine and so are less likely to cross the blood-brain barrier; they are also less well absorbed from the gastro-intestinal tract.

Dicycloverine hydrochloride may also have some direct action on smooth muscle. Hyoscine butylbromide is advocated as a gastro-intestinal antispasmodic, but it is poorly absorbed; the injection may be useful in endoscopy and radiology.

Cautions Antimuscarinics should be used with caution in children (especially children with Down's syndrome) due to increased risk of side-effects; they should also be used with caution in autonomic neuropathy, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery), pyrexia, and in children susceptible to angle-closure glaucoma. Antimuscarinics are not used in children with gastro-oesophageal reflux disease, diarrhoea or ulcerative colitis. **Interactions:** Appendix 1 (antimuscarinics).

Contra-indications Antimuscarinics are contra-indicated in myasthenia gravis (but may be used to decrease muscarinic side-effects of anticholinesterases—section 10.2.1), paralytic ileus, pyloric stenosis, and toxic megacolon.

Side-effects Side-effects of antimuscarinics include constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin. Side-effects that occur occasionally include nausea, vomiting, and giddiness; very rarely, angle closure glaucoma may occur.

DICYCLOVERINE HYDROCHLORIDE

(Dicyclomine hydrochloride)

Cautions see notes above

Contra-indications see notes above; child under 6 months

Pregnancy not known to be harmful; manufacturer advises use only if essential

Breast-feeding avoid—present in milk; apnoea reported in infant

Side-effects see notes above

Indications and dose

Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

• By mouth

Child 6 months–2 years 5–10 mg 3–4 times daily 15 minutes before feeds

Child 2–12 years 10 mg 3 times daily

Child 12–18 years 10–20 mg 3 times daily

Dicycloverine (Non-proprietary) (PoM)

Tablets, dicycloverine hydrochloride 10 mg, net price 100-tab pack = £51.50; 20 mg, 84-tab pack = £55.20

Syrup, dicycloverine hydrochloride 10 mg/5 mL, net price 120 mL = £56.05

Note Dicycloverine hydrochloride can be sold to the public provided that max. single dose is 10 mg and max. daily dose is 60 mg

Compound preparations

Kolanticon® (Peckforton)

Gel, sugar-free, dicycloverine hydrochloride 2.5 mg, dried aluminium hydroxide 200 mg, light magnesium oxide 100 mg, simeticone 20 mg/5 mL, net price 200 mL = £2.21, 500 mL = £3.94

Dose

Child 12–18 years 10–20 mL every 4 hours when required

HYOSCINE BUTYLBROMIDE

Cautions see notes above; also intestinal and urinary outlet obstruction

Contra-indications see notes above

Pregnancy manufacturer advises avoid

Breast-feeding amount too small to be harmful

Side-effects see notes above

Licensed use *tablets* not licensed for use in children under 6 years; *injection* not licensed for use in children (age range not specified by manufacturer)

Indications and dose

Symptomatic relief of gastro-intestinal or genito-urinary disorders characterised by smooth muscle spasm

• By mouth

Child 6–12 years 10 mg 3 times daily

Child 12–18 years 20 mg 4 times daily

Excessive respiratory secretions and bowel colic in palliative care (see also p. 19)

• By mouth

Child 1 month–2 years 300–500 micrograms/kg (max. 5 mg) 3–4 times daily

Child 2–5 years 5 mg 3–4 times daily

Child 5–12 years 10 mg 3–4 times daily

Child 12–18 years 10–20 mg 3–4 times daily

• By intramuscular or intravenous injection

Child 1 month–4 years 300–500 micrograms/kg (max. 5 mg) 3–4 times daily

Child 5–12 years 5–10 mg 3–4 times daily

Child 12–18 years 10–20 mg 3–4 times daily

Acute spasm, spasm in diagnostic procedures

- By intramuscular or intravenous injection

Child 2–6 years 5 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), max. 15 mg daily

Child 6–12 years 5–10 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), max. 30 mg daily

Child 12–18 years 20 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), max. 80 mg daily

Administration for intravenous injection, may be diluted with Glucose 5% or Sodium Chloride 0.9%; give over at least 1 minute.

For administration by mouth, injection solution may be used; content of ampoule may be stored in a refrigerator for up to 24 hours after opening

Buscopan® (Boehringer Ingelheim) (PoM)

Tablets, coated, hyoscine butylbromide 10 mg, net price 56-tab pack = £3.00

Note Hyoscine butylbromide tablets can be sold to the public for medically confirmed irritable bowel syndrome, provided single dose does not exceed 20 mg, daily dose does not exceed 80 mg, and pack does not contain a total of more than 240 mg

Injection, hyoscine butylbromide 20 mg/mL. Net price 1-mL amp = 29p

PROPANTHELINE BROMIDE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy manufacturer advises avoid unless essential

Breast-feeding may suppress lactation

Side-effects see notes above

Licensed use tablets not licensed for use in children under 12 years

Indications and dose

Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

- By mouth

Child 1 month–12 years 300 micrograms/kg (max. 15 mg) 3–4 times daily at least one hour before food

Child 12–18 years 15 mg 3 times daily at least one hour before meals and 30 mg at night (max. 120 mg daily)

Pro-Banthine® (Archimedes) (PoM)

Tablets, pink, s/c, propantheline bromide 15 mg, net price 112-tab pack = £20.74. Label: 23

Other antispasmodics

Alverine, mebeverine, and peppermint oil are believed to be direct relaxants of intestinal smooth muscle and may relieve pain in *irritable bowel syndrome* and primary dysmenorrhoea. They have no serious adverse effects; peppermint oil occasionally causes heartburn.

ALVERINE CITRATE

Contra-indications paralytic ileus

Pregnancy use with caution

Breast-feeding manufacturer advises avoid—limited information available

Side-effects nausea; dyspnoea; headache, dizziness; pruritus, rash; hepatitis also reported

Indications and dose

Adjunct in gastro-intestinal disorders characterised by smooth muscle spasm, dysmenorrhoea

- By mouth

Child 12–18 years 60–120 mg 1–3 times daily

Spasmonal® (Meda)

Capsules, alverine citrate 60 mg (blue/grey), net price 100-cap pack = £16.45; 120 mg (*Spasmonal® Forte*, blue/grey), 60-cap pack = £19.42

MEBEVERINE HYDROCHLORIDE

Contra-indications paralytic ileus

Pregnancy not known to be harmful—manufacturers advise avoid

Breast-feeding manufacturers advise avoid—no information available

Side-effects allergic reactions (including rash, urticaria, angioedema) reported

Licensed use tablets and liquid not licensed for use in children under 10 years; granules not licensed for use in children under 12 years; modified-release capsules not licensed for use in children under 18 years

Indications and dose

Adjunct in gastro-intestinal disorders characterised by smooth muscle spasm

- By mouth

Child 3–4 years 25 mg 3 times daily, preferably 20 minutes before meals

Child 4–8 years 50 mg 3 times daily, preferably 20 minutes before meals

Child 8–10 years 100 mg 3 times daily, preferably 20 minutes before meals

Child 10–18 years 135–150 mg 3 times daily, preferably 20 minutes before meals

Mebeverine Hydrochloride (Non-proprietary) (PoM)

Tablets, mebeverine hydrochloride 135 mg, net price 100-tab pack = £5.06. Counselling, administration

Oral suspension, mebeverine hydrochloride (as mebeverine embonate) 50 mg/5 mL, net price 300 mL = £143.43. Counselling, administration

Colofac® (Abbott Healthcare) (PoM)

Tablets, s/c, mebeverine hydrochloride 135 mg, net price 100-tab pack = £7.52. Counselling, administration

Modified release

Colofac® MR (Abbott Healthcare) (PoM)

Capsules, m/r, mebeverine hydrochloride 200 mg, net price 60-cap pack = £6.92. Label: 25

Dose

Irritable bowel syndrome

- By mouth

Child 12–18 years 1 capsule twice daily

Compound preparations

Fybogel® Mebeverine (Reckitt Benckiser)

Granules, buff, effervescent, ispaghula husk 3.5 g, mebeverine hydrochloride 135 mg/sachet, net price 10 sachets = £3.75. Label: 13, 22, counselling, see below

Excipients include aspartame (section 9.4.1)

Electrolytes K⁺ 7 mmol/sachet

Dose

Irritable bowel syndrome

- By mouth

Child 12–18 years 1 sachet in water, morning and evening 30 minutes before food; an additional sachet may also be taken before the midday meal if necessary

Counselling Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed

PEPPERMINT OIL

Cautions sensitivity to menthol

Pregnancy not known to be harmful

Breast-feeding significant levels of menthol in breast milk unlikely

Side-effects heartburn, perianal irritation; rarely, allergic reactions (including rash, headache, bradycardia, muscle tremor, ataxia)

Local irritation Capsules should not be broken or chewed because peppermint oil may irritate mouth or oesophagus

Indications and dose

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

- By mouth

Child 15–18 years 1–2 capsules, swallowed whole with water, 3 times daily for up to 3 months if necessary

Colpermin® (McNeil)

Capsules, e/c, light blue/dark blue, blue band, peppermint oil 0.2 mL. Net price 100-cap pack = £12.05. Label: 5, 25

Excipients include arachis (peanut) oil

Motility stimulants

A low dose of **erythromycin** stimulates gastro-intestinal motility and may be used on the advice of a paediatric gastroenterologist to promote tolerance of enteral feeds; erythromycin may be less effective as a prokinetic drug in preterm neonates than in older children.

ERYTHROMYCIN

Cautions see section 5.1.5; **interactions:** Appendix 1 (macrolides)

Side-effects see section 5.1.5

Licensed use not licensed for use in gastro-intestinal stasis

Indications and dose

Gastro-intestinal stasis

- By mouth

Neonate 3 mg/kg 4 times daily

Child 1 month–18 years 3 mg/kg 4 times daily

- By intravenous infusion

Neonate 3 mg/kg 4 times daily

Child 1 month–1 year 3 mg/kg 4 times daily

Preparations

Section 5.1.5

1.3 Antisecretory drugs and mucosal protectants

1.3.1 H₂-receptor antagonists

1.3.2 Selective antimuscarinics

1.3.3 Chelates and complexes

1.3.4 Prostaglandin analogues

1.3.5 Proton pump inhibitors

Peptic ulceration commonly involves the stomach, duodenum, and lower oesophagus; after gastric surgery it involves the gastro-enterostomy stoma.

Healing can be promoted by general measures, stopping smoking and taking antacids and by antisecretory drug treatment, but relapse is common when treatment ceases. Nearly all duodenal ulcers and most gastric ulcers not associated with NSAIDs are caused by *Helicobacter pylori*.

The management of *H. pylori* infection and of NSAID-associated ulcers is discussed below.

Helicobacter pylori infection

Eradication of *Helicobacter pylori* reduces the recurrence of gastric and duodenal ulcers and the risk of rebleeding. The presence of *H. pylori* should be confirmed before starting eradication treatment. If possible, the antibacterial sensitivity of the organism should be established at the time of endoscopy and biopsy. Acid inhibition combined with antibacterial treatment is highly effective in the eradication of *H. pylori*; reinfection is rare. Antibiotic-associated colitis is an uncommon risk.

Treatment to eradicate *H. pylori* infection in children should be initiated under specialist supervision. One-week triple-therapy regimens that comprise omeprazole, amoxicillin, and either clarithromycin or metronidazole are recommended. Resistance to clarithromycin or to metronidazole is much more common than to amoxicillin and can develop during treatment. A regimen containing amoxicillin and clarithromycin is therefore recommended for initial therapy and one containing amoxicillin and metronidazole is recommended for eradication failure or for a child who has been treated with a macrolide for other infections. There is usually no need to continue antisecretory treatment (with a proton pump inhibitor or H₂-receptor antagonist); however, if the ulcer is large, or complicated by haemorrhage or perforation then antisecretory treatment is continued for a further 3 weeks. Lansoprazole may be considered if omeprazole is unsuitable. Treatment failure usually indicates antibacterial resistance or poor compliance.

Two-week triple-therapy regimens offer the possibility of higher eradication rates compared to one-week regimens, but adverse effects are common and poor compliance is likely to offset any possible gain.

Two-week dual-therapy regimens using a proton pump inhibitor and a single antibacterial produce low rates of *H. pylori* eradication and are **not** recommended.

For the role of *H. pylori* eradication therapy in children starting or taking NSAIDs, see NSAID-associated ulcers, below.

Recommended regimens for *Helicobacter pylori* eradication

Eradication therapy	Age range	Oral dose (to be used in combination with omeprazole, section 1.3.5)
Amoxicillin	1–6 years	250 mg twice daily (with clarithromycin)
		125 mg 3 times daily (with metronidazole)
	6–12 years	500 mg twice daily (with clarithromycin)
		250 mg 3 times daily (with metronidazole)
	12–18 years	1 g twice daily (with clarithromycin)
		500 mg 3 times daily (with metronidazole)
Clarithromycin	1–12 years	7.5 mg/kg (max. 500 mg) twice daily (with metronidazole or amoxicillin)
	12–18 years	500 mg twice daily (with metronidazole or amoxicillin)
Metronidazole	1–6 years	100 mg twice daily (with clarithromycin)
		100 mg 3 times daily (with amoxicillin)
	6–12 years	200 mg twice daily (with clarithromycin)
		200 mg 3 times daily (with amoxicillin)
	12–18 years	400 mg twice daily (with clarithromycin)
		400 mg 3 times daily (with amoxicillin)

Test for *Helicobacter pylori*

¹³C-Urea breath test kits are available for confirming the presence of gastro-duodenal infection with *Helicobacter pylori*. The test involves collection of breath samples before and after ingestion of an oral solution of ¹³C-urea; the samples are sent for analysis by an appropriate laboratory. The test should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of treatment with an antisecretory drug. A specific ¹³C-Urea breath test kit for children is available (*Helicobacter Test INFAI for children of the age 3–11*®). However the appropriateness of testing for *H. pylori* infection in children has not been established. Breath, saliva, faecal, and urine tests for *H. pylori* are frequently unreliable in children; the most accurate method of diagnosis is endoscopy with biopsy.

Helicobacter Test INFAI for children of the age 3–11® (Infai) (PoM)

Oral powder, ¹³C-urea 45 mg, net price 1 kit (including 4 breath sample containers, straws) = £19.20 (spectrometric analysis included)

Helicobacter Test INFAI® (Infai) (PoM)

Oral powder, ¹³C-urea 75 mg, net price 1 kit (including 4 breath-sample containers, straws) = £19.75 (spectrometric analysis included); 1 kit (including 2 breath bags) = £19.20 (spectroscopic analysis not included); 50-test set = £855.00 (spectrometric analysis included)

NSAID-associated ulcers

Gastro-intestinal bleeding and ulceration can occur with NSAID use (section 10.1.1). In adults, the risk of serious upper gastro-intestinal side-effects varies between individual NSAIDs (see Gastro-intestinal side-effects, p. 506). Whenever possible, NSAIDs should be **with-drawn** if an ulcer occurs.

Children at high risk of developing gastro-intestinal complications with a NSAID include those with a history of peptic ulcer disease or serious upper gastro-intestinal complication, those taking other medicines that increase the risk of upper gastro-intestinal side-effects, or those with serious co-morbidity. In children at risk of ulceration, a proton pump inhibitor (section 1.3.5) can

be considered for protection against gastric and duodenal ulcers associated with non-selective NSAIDs; high dose ranitidine is an alternative.

NSAID use and *H. pylori* infection are independent risk factors for gastro-intestinal bleeding and ulceration. In children already taking a NSAID, eradication of *H. pylori* is unlikely to reduce the risk of NSAID-induced bleeding or ulceration. However, in children about to start long-term NSAID treatment who are *H. pylori* positive and have dyspepsia or a history of gastric or duodenal ulcer, eradication of *H. pylori* may reduce the overall risk of ulceration.

If the NSAID can be discontinued in a child who has developed an ulcer, a proton pump inhibitor usually produces the most rapid healing; alternatively the ulcer can be treated with an H₂-receptor antagonist.

If NSAID treatment needs to continue, the ulcer is treated with a proton pump inhibitor (section 1.3.5).

1.3.1 H₂-receptor antagonists

Histamine H₂-receptor antagonists heal *gastric and duodenal ulcers* by reducing gastric acid output as a result of histamine H₂-receptor blockade; they are also used to relieve symptoms of *dyspepsia and gastro-oesophageal reflux disease* (section 1.1). H₂-receptor antagonists should not normally be used for *Zollinger–Ellison syndrome* because proton pump inhibitors (section 1.3.5) are more effective.

Maintenance treatment with low doses has largely been replaced in *Helicobacter pylori* positive children by eradication regimens (section 1.3).

H₂-receptor antagonist therapy can promote healing of *NSAID-associated ulcers* (section 1.3).

Treatment with a H₂-receptor antagonist has not been shown to be beneficial in haematemesis and melaena, but prophylactic use reduces the frequency of bleeding from *gastroduodenal erosions in hepatic coma*, and possibly in other conditions requiring intensive care. Treatment also reduces the risk of *acid aspiration* in obstetric patients at delivery (Mendelson's syndrome).

H₂-receptor antagonists are also used to reduce the degradation of pancreatic enzyme supplements (section 1.9.4) in children with cystic fibrosis.

Side-effects Side-effects of H₂-receptor antagonists include diarrhoea, headache, and dizziness. Rash (including erythema multiforme and toxic epidermal necrolysis) occurs less frequently. Other side-effects reported rarely or very rarely include hepatitis, cholestatic jaundice, bradycardia, psychiatric reactions (including confusion, depression, and hallucinations) particularly in the very ill, blood disorders (including leucopenia, thrombocytopenia, and pancytopenia), arthralgia, and myalgia. There are isolated reports of gynaecomastia and impotence.

RANITIDINE

Cautions interactions: Appendix 1 (histamine H₂-antagonists)

Renal impairment use half normal dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid unless essential, but not known to be harmful

Breast-feeding significant amount present in milk, but not known to be harmful

Side-effects see notes above; also *less commonly* blurred vision; also reported pancreatitis, involuntary movement disorders, interstitial nephritis, alopecia

Licensed use *oral* preparations not licensed for use in children under 3 years; *injection* not licensed for use in children under 6 months

Indications and dose

Reflux oesophagitis, benign gastric and duodenal ulceration, prophylaxis of stress ulceration, other conditions where gastric acid reduction is beneficial (see notes above and section 1.9.4)

• By mouth

Neonate 2 mg/kg 3 times daily but absorption unreliable; max. 3 mg/kg 3 times daily

Child 1–6 months 1 mg/kg 3 times daily; max. 3 mg/kg 3 times daily

Child 6 months–3 years 2–4 mg/kg twice daily

Child 3–12 years 2–4 mg/kg (max. 150 mg) twice daily; increased up to 5 mg/kg (max. 300 mg) twice daily in severe gastro-oesophageal reflux disease

Child 12–18 years 150 mg twice daily or 300 mg at night; increased if necessary, to 300 mg twice daily or 150 mg 4 times daily for up to 12 weeks in moderate to severe gastro-oesophageal reflux disease

Note In fat malabsorption syndrome, give 1–2 hours before food to enhance effects of pancreatic enzyme replacement

• By slow intravenous injection

Neonate 0.5–1 mg/kg every 6–8 hours

Child 1 month–18 years 1 mg/kg (max. 50 mg) every 6–8 hours (may be given as an intermittent infusion at a rate of 25 mg/hour)

Administration For *slow intravenous injection* dilute to a concentration of 2.5 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over at least 3 minutes

Ranitidine (Non-proprietary) (PoM)

Tablets, ranitidine (as hydrochloride) 150 mg, net price 60-tab pack = £1.27; 300 mg, 30-tab pack = £2.09

Brands include *Ranitic*®

Effervescent tablets, ranitidine (as hydrochloride) 150 mg, net price 60-tab pack = £23.89; 300 mg, 30-tab pack = £23.89. Label: 13

Excipients may include sodium (check with supplier)

Oral solution, ranitidine (as hydrochloride) 75 mg/5 mL, net price 100 mL = £2.75, 300 mL = £7.25

Excipients may include alcohol (check with supplier)

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Note Ranitidine can be sold to the public for children over 16 years (provided packs do not contain more than 2 weeks' supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for the prevention of these symptoms when associated with consumption of food or drink (max. single dose 75 mg, max. daily dose 300 mg)

Injection, ranitidine (as hydrochloride) 25 mg/mL, net price 2-mL amp = 54p

Zantac® (GSK) (PoM)

Tablets, f/c, ranitidine (as hydrochloride) 150 mg, net price 60-tab pack = £1.30; 300 mg, 30-tab pack = £1.30

Syrup, sugar-free, ranitidine (as hydrochloride) 75 mg/5 mL. Net price 300 mL = £20.76

Excipients include alcohol 8%

Injection, ranitidine (as hydrochloride) 25 mg/mL. Net price 2-mL amp = 56p

1.3.2 Selective antimuscarinics

Classification not used in *BNF for Children*.

1.3.3 Chelates and complexes

Sucralfate is a complex of aluminium hydroxide and sulfated sucrose that appears to act by protecting the mucosa from acid-pepsin attack; it has minimal antacid properties. Sucralfate can be used to prevent stress ulceration in children receiving intensive care. It should be used with caution in this situation (**important**: reports of bezoar formation, see Bezoar Formation below).

SUCRALFATE

Cautions administration of sucralfate and enteral feeds should be separated by 1 hour; **interactions**: Appendix 1 (sucralfate)

Bezoar formation Following reports of bezoar formation associated with sucralfate, caution is advised in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying

Renal impairment use with caution; aluminium is absorbed and may accumulate

Pregnancy no evidence of harm; absorption from gastro-intestinal tract negligible

Breast-feeding amount probably too small to be harmful

Side-effects constipation; *less frequently* diarrhoea, nausea, indigestion, flatulence, gastric discomfort, back pain, dizziness, headache, drowsiness, bezoar formation (see above), dry mouth, and rash

Licensed use not licensed for use in children under 15 years; tablets not licensed for prophylaxis of stress ulceration

Indications and dose

Prophylaxis of stress ulceration in child under intensive care

• By mouth

Child 1 month–2 years 250 mg 4–6 times daily

Child 2–12 years 500 mg 4–6 times daily

Child 12–15 years 1 g 4–6 times daily

Child 15–18 years 1 g 6 times daily; max. 8 g daily

Benign gastric and duodenal ulceration

• By mouth

Child 1 month–2 years 250 mg 4–6 times daily

Child 2–12 years 500 mg 4–6 times daily

Child 12–15 years 1 g 4–6 times daily

Child 15–18 years 2 g twice daily (on rising and at bedtime) or 1 g 4 times daily (1 hour before meals and at bedtime) taken for 4–6 weeks, or in resistant cases up to 12 weeks; max. 8 g daily

Administration for administration by mouth, sucral-fate should be given 1 hour before meals, see also Cautions, above; oral suspension blocks fine-bore feeding tubes; crushed tablets may be dispersed in water.

Antepsin® (Chugai) (PoM)

Tablets, scored, sucral-fate 1 g, net price 50-tab pack = £6.36. Label: 5

Suspension, sucral-fate, 1 g/5 mL, net price 250 mL (aniseed- and caramel-flavoured) = £6.36. Label: 5

1.3.4 Prostaglandin analogues

Classification not used in *BNF for Children*.

1.3.5 Proton pump inhibitors

Proton pump inhibitors inhibit gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the 'proton pump') of the gastric parietal cell. **Omeprazole** is an effective short-term treatment for gastric and duodenal ulcers; it is also used in combination with antibacterials for the eradication of *Helicobacter pylori* (see p. 41 for specific regimens). An initial short course of omeprazole is the treatment of choice in gastro-oesophageal reflux disease with severe symptoms; children with endoscopically confirmed erosive, ulcerative, or stricturing oesophagitis usually need to be maintained on omeprazole.

Omeprazole is also used for the prevention and treatment of NSAID-associated ulcers (see p. 41). In children who need to continue NSAID treatment after an ulcer has healed, the dose of omeprazole should not normally be reduced because asymptomatic ulcer deterioration may occur.

Omeprazole is effective in the treatment of the *Zollinger-Ellison syndrome* (including cases resistant to other treatment). It is also used to reduce the degradation of pancreatic enzyme supplements (section 1.9.4) in children with cystic fibrosis.

Lansoprazole is not licensed for use in children, but may be considered when the available formulations of omeprazole are unsuitable.

Esomeprazole can be used for the management of gastro-oesophageal reflux disease when the available formulations of omeprazole and lansoprazole are unsuitable.

Cautions Patients at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D and, if necessary, receive other preventative therapy (see section 6.6). Measurement of serum-magnesium concentrations should be considered before and during prolonged treatment with a proton pump inhibitor, especially when used with other drugs that cause hypomagnesaemia or with digoxin. A proton pump inhibitor should be prescribed for appropriate indications at the lowest effective dose for the shortest period; the need for long-term treatment should be reviewed periodically.

Side-effects Side-effects of the proton pump inhibitors include gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, flatulence, diarrhoea, constipation), and headache. Less frequent side-effects include dry mouth, peripheral oedema, dizziness, sleep disturbances, fatigue, paraesthesia, arthralgia, myalgia, rash, and pruritus. Other side-effects reported rarely or very rarely include taste disturbance, stomatitis, hepatitis, jaundice, hypersensitivity reactions (including anaphylaxis, bronchospasm), fever, depression, hallucinations, confusion, gynaecomastia, interstitial nephritis, hyponatraemia, hypomagnesaemia (usually after 1 year of treatment, but sometimes after 3 months of treatment), blood disorders (including leucopenia, leucocytosis, pancytopenia, thrombocytopenia), visual disturbances, sweating, photosensitivity, alopecia, Stevens-Johnson syndrome, and toxic epidermal necrolysis. By decreasing gastric acidity, proton pump inhibitors may increase the risk of gastro-intestinal infections (including *Clostridium difficile* infection).

Rebound acid hypersecretion and protracted dyspepsia may occur after stopping prolonged treatment with a proton pump inhibitor.

ESOMEPRAZOLE

Cautions interactions: Appendix 1 (proton pump inhibitors)

Hepatic impairment **child 1–12 years** max. 10 mg daily in severe impairment; **child 12–18 years** max. 20 mg daily in severe impairment

Renal impairment manufacturer advises caution in severe renal insufficiency

Pregnancy manufacturer advises caution—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above

Licensed use tablets and capsules not licensed for use in children 1–12 years

Indications and dose

Gastro-oesophageal reflux disease (in the presence of erosive reflux oesophagitis)

• By mouth

Child 1–12 years

Body-weight 10–20 kg 10 mg once daily for 8 weeks

Body-weight over 20 kg 10–20 mg once daily for 8 weeks

Child 12–18 years 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or

symptoms persist; maintenance 20 mg daily

- By intravenous injection over at least 3 minutes or by intravenous infusion

Child 1–12 years

Body-weight under 20 kg 10 mg once daily

Body-weight over 20 kg 10–20 mg once daily

Child 12–18 years 40 mg once daily

Symptomatic treatment of gastro-oesophageal reflux disease (in the absence of oesophagitis)

- By mouth

Child 1–12 years, body-weight over 10 kg 10 mg once daily for up to 8 weeks

Child 12–18 years 20 mg once daily for up to 4 weeks

- By intravenous injection over at least 3 minutes or by intravenous infusion

Child 1–12 years 10 mg once daily

Child 12–18 years 20 mg once daily

Administration for intravenous infusion, dilute reconstituted solution to a concentration not exceeding 800 micrograms/mL with Sodium Chloride 0.9%; give over 10–30 minutes

Esomeprazole (Non-proprietary) (PoM)

Capsules, enclosing e/c pellets, esomeprazole (as magnesium salt) 20 mg, net price 28-cap pack = £4.50; 40 mg, 28-cap pack = £5.42. Counselling, administration

Brands include Eموزول®

Administration Do not chew or crush capsules; swallow whole or mix capsule contents in water and drink within 30 minutes; for administration through a gastric tube, consult product literature

Tablets, e/c, esomeprazole (as magnesium salt) 20 mg, net price 28-tab pack = £3.70; 40 mg, 28-tab pack = £4.58. Counselling, administration

Administration Do not chew or crush tablets; swallow whole or disperse in water and drink within 30 minutes; for administration through a gastric tube, consult product literature

Injection, powder for reconstitution, esomeprazole (as sodium salt), net price 40-mg vial = £3.10

Nexium® (AstraZeneca) (PoM)

Tablets, e/c, f/c, esomeprazole (as magnesium trihydrate) 20 mg (light pink), net price 28-tab pack = £18.50; 40 mg (pink), 28-tab pack = £25.19. Counselling, administration

Administration Do not chew or crush tablets; swallow whole or disperse in water and drink within 30 minutes; for administration through a gastric tube, consult product literature

Granules, yellow, e/c, esomeprazole (as magnesium trihydrate) 10 mg/sachet, net price 28-sachet pack = £25.19. Label: 25, counselling, administration

Administration Disperse the contents of each sachet in approx. 15 mL water. Stir and leave to thicken for a few minutes; stir again before administration and use within 30 minutes; rinse container with 15 mL water to obtain full dose; for administration through gastric tube, consult product literature

Injection, powder for reconstitution, esomeprazole (as sodium salt), net price 40-mg vial = £4.25

LANSOPRAZOLE

Cautions interactions: Appendix 1 (proton pump inhibitors)

Hepatic impairment use half normal dose in moderate to severe liver disease

Pregnancy manufacturer advises avoid

Breast-feeding avoid —present in milk in animal studies

Side-effects see notes above; also glossitis, pancreatitis, anorexia, restlessness, tremor, impotence, petechiae, and purpura; very rarely colitis, raised serum cholesterol or triglycerides

Licensed use not licensed for use in children

Indications and dose

Gastro-oesophageal reflux disease, acid-related dyspepsia, treatment of duodenal and benign gastric ulcer including those complicating NSAID therapy, fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis

- By mouth

Child body-weight under 30 kg 0.5–1 mg/kg (max. 15 mg) once daily in the morning

Child body-weight over 30 kg 15–30 mg once daily in the morning

Administration for administration by a nasogastric tube or an oral syringe, Zoton FasTab® can be dispersed in a small amount of water

Zoton® (Pfizer) (PoM)

FasTab® (= orodispersible tablet), lansoprazole

15 mg, net price 28-tab pack = £2.99; 30 mg, 28-tab pack = £5.50. Label: 5, 22, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling Tablets should be placed on the tongue, allowed to disperse and swallowed, or may be swallowed whole with a glass of water.

OMEPRAZOLE

Cautions interactions: Appendix 1 (proton pump inhibitors)

Hepatic impairment no more than 700 micrograms/kg (max. 20 mg) once daily

Pregnancy not known to be harmful

Breast-feeding present in milk but not known to be harmful

Side-effects see notes above; also agitation and impotence

Licensed use capsules and tablets not licensed for use in children except for severe ulcerating reflux oesophagitis in children over 1 year; injection not licensed for use in children under 12 years

Indications and dose

Gastro-oesophageal reflux disease, acid-related dyspepsia, treatment of duodenal and benign gastric ulcers including those complicating NSAID therapy, Zollinger-Ellison syndrome, fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis

- By mouth

Neonate 700 micrograms/kg once daily, increased if necessary after 7–14 days to 1.4 mg/kg; some neonates may require up to 2.8 mg/kg once daily

Child 1 month–2 years 700 micrograms/kg once daily, increased if necessary to 3 mg/kg (max. 20 mg) once daily

Child body-weight 10–20 kg 10 mg once daily increased if necessary to 20 mg once daily (in

severe ulcerating reflux oesophagitis, max. 12 weeks at higher dose)

Child body-weight over 20 kg 20 mg once daily increased if necessary to 40 mg once daily (in severe ulcerating reflux oesophagitis, max. 12 weeks at higher dose)

- **By intravenous injection over 5 minutes** or by intravenous infusion

Child 1 month–12 years initially 500 micrograms/kg (max. 20 mg) once daily, increased to 2 mg/kg (max. 40 mg) once daily if necessary

Child 12–18 years 40 mg once daily

***Helicobacter pylori* eradication** (in combination with antibiotics see p. 41)

- **By mouth**

Child 1–12 years 1–2 mg/kg (max. 40 mg) once daily

Child 12–18 years 40 mg once daily

Administration for administration *by mouth*, swallow whole, or disperse *Losec MUPS*® tablets in water, or mix capsule contents or *Losec MUPS*® tablets with fruit juice or yoghurt. Preparations consisting of an e/c tablet within a capsule should **not** be opened.

For administration through an *enteral feeding tube*, use *Losec MUPS*® or the contents of a capsule containing omeprazole dispersed in a large volume of water, or in 10 mL Sodium Bicarbonate 8.4% (1 mmol Na⁺/mL) (allow to stand for 10 minutes before administration).

For *intermittent intravenous infusion*, dilute reconstituted solution to a concentration of 400 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; give over 20–30 minutes

Omeprazole (Non-proprietary) (PoM)

Capsules, enclosing e/c granules, omeprazole 10 mg, net price 28-cap pack = £1.15; 20 mg, 28-cap pack = £1.15; 40 mg, 7-cap pack = £1.12, 28-cap pack = £4.98. Counselling, administration

Note Some preparations consist of an e/c tablet within a capsule

Dental prescribing on NHS Gastro-resistant omeprazole capsules may be prescribed

Tablets, e/c, omeprazole 10 mg, net price 28-tab pack = £7.85; 20 mg, 28-tab pack = £5.46; 40 mg, 7-tab pack = £4.90. Label: 25

Intravenous infusion, powder for reconstitution, omeprazole (as sodium salt), net price 40-mg vial = £4.16

Losec® (AstraZeneca) (PoM)

MUPS® (multiple-unit pellet system = dispersible tablets), f/c, omeprazole 10 mg (light pink), net price 28-tab pack = £7.75; 20 mg (pink), 28-tab pack = £11.60; 40 mg (red-brown), 7-tab pack = £5.80. Counselling, administration

Capsules, enclosing e/c granules, omeprazole 10 mg (pink), net price 28-cap pack = £9.30; 20 mg (pink/brown), 28-cap pack = £13.92; 40 mg (brown), 7-cap pack = £6.96. Counselling, administration

Intravenous infusion, powder for reconstitution, omeprazole (as sodium salt), net price 40-mg vial = £6.50

Injection, powder for reconstitution, omeprazole (as sodium salt), net price 40-mg vial (with solvent) = £6.49

1.4 Acute diarrhoea

1.4.1 Adsorbents and bulk-forming drugs

1.4.2 Antimotility drugs

1.4.3 Enkephalinase inhibitors

The priority in acute diarrhoea, as in gastro-enteritis, is the prevention or reversal of fluid and electrolyte depletion—this is particularly important in infants. For details of **oral rehydration preparations**, see section 9.2.1.2. Severe dehydration requires immediate admission to hospital and urgent replacement of fluid and electrolytes.

Antimotility drugs (section 1.4.2) relieve symptoms of diarrhoea. They are used in the management of uncomplicated acute diarrhoea in adults, but are **not** recommended for use in children under 12 years. Fluid and electrolyte replacement (section 9.2.1.2) are of prime importance in the treatment of acute diarrhoea.

Racecadotril (section 1.4.3) is licensed, as an adjunct to rehydration, for the symptomatic treatment of uncomplicated acute diarrhoea; however, it should only be used when usual supportive measures, including oral rehydration, are insufficient to control the condition.

Antispasmodics (section 1.2) are occasionally of value in treating abdominal cramp associated with diarrhoea but they should **not** be used for primary treatment. Antispasmodics and antiemetics should be **avoided** in young children with gastro-enteritis since they are rarely effective and have troublesome side-effects.

Antibacterial drugs are generally unnecessary in simple gastro-enteritis because the complaint usually resolves quickly without such treatment, and infective diarrhoeas in the UK often have a viral cause. Systemic bacterial infection does, however, need appropriate systemic treatment; for drugs used in campylobacter enteritis, shigellosis, and salmonellosis, see p. 248

Colestyramine (section 1.9.2) binds unabsorbed bile salts and provides symptomatic relief of diarrhoea following ileal disease or resection.

1.4.1 Adsorbents and bulk-forming drugs

Adsorbents such as kaolin are **not** recommended for *acute diarrhoeas*. Bulk-forming drugs, such as ispaghula, methylcellulose, and sterculia (section 1.6.1) are rarely effective in controlling faecal consistency in ileostomy and colostomy.

1.4.2 Antimotility drugs

Antimotility drugs prolong the duration of intestinal transit by binding to opioid receptors in the gastro-intestinal tract. Loperamide does not cross the blood-brain barrier readily. Antimotility drugs have a role in the management of uncomplicated *acute diarrhoea* in adults but not in children under 12 years; see also section 1.4. However, in the case of dehydration, fluid and electrolyte replacement (section 9.2.1.2) are of primary importance.

For comments on their role in *chronic bowel disorders* see section 1.5. Antimotility drugs are also used in children with *stoma* (section 1.8).

CODEINE PHOSPHATE

Cautions see section 4.7.2; tolerance and dependence may occur with prolonged use; **interactions:** Appendix 1 (opioid analgesics)

Contra-indications see section 4.7.2; also conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic-associated colitis

Hepatic impairment section 4.7.2

Renal impairment section 4.7.2

Pregnancy section 4.7.2

Breast-feeding section 4.7.2

Side-effects section 4.7.2

Indications and dose

Diarrhoea (but see notes above)

• By mouth

Child 12–18 years 30 mg (range 15–60 mg) 3–4 times daily

Pain section 4.7.2

■ **Preparations**

Section 4.7.2

CO-PHENOTROPE

A mixture of diphenoxylate hydrochloride and atropine sulfate in the mass proportions 100 parts to 1 part respectively

Cautions section 4.7.2; also young children are particularly susceptible to **overdosage** and symptoms may be delayed and observation is needed for at least 48 hours after ingestion; presence of subclinical doses of atropine may give rise to atropine side-effects in susceptible individuals or in overdosage (section 1.2); **interactions:** Appendix 1 (antimuscarinics, opioid analgesics)

Contra-indications section 4.7.2 and also see under Antimuscarinics (section 1.2)

Hepatic impairment section 4.7.2; also avoid in jaundice

Renal impairment section 4.7.2

Pregnancy section 4.7.2

Breast-feeding may be present in milk

Side-effects section 4.7.2 and also see under Antimuscarinics (section 1.2); also abdominal pain, anorexia, fever

Licensed use not licensed for use in children under 4 years

Indications and dose

See preparations

Administration for administration *by mouth* tablets may be crushed

Co-phenotrope (Non-proprietary) **[POM]**

Tablets, co-phenotrope 2.5/0.025 (diphenoxylate hydrochloride 2.5 mg, atropine sulfate 25 micrograms), net price 100 = £10.74

Brands include *Lomotil*®

Dose

Control of faecal consistency after colostomy or ileostomy, adjunct to rehydration in acute diarrhoea (but see notes above)

• By mouth

Child 2–4 years half tablet 3 times daily

Child 4–9 years 1 tablet 3 times daily

Child 9–12 years 1 tablet 4 times daily

Child 12–16 years 2 tablets 3 times daily

Child 16–18 years initially 4 tablets then 2 tablets 4 times daily

Note Co-phenotrope 2.5/0.025 can be sold to the public for children over 16 years (provided packs do not contain more than 20 tablets) as an adjunct to rehydration in acute diarrhoea (max. daily dose 10 tablets)

LOPERAMIDE HYDROCHLORIDE

Cautions see notes above; **interactions:** Appendix 1 (loperamide)

Contra-indications conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in conditions such as active ulcerative colitis or antibiotic-associated colitis

Hepatic impairment risk of accumulation—manufacturer advises caution

Pregnancy manufacturer advises avoid—no information available

Breast-feeding amount probably too small to be harmful

Side-effects nausea, flatulence, headache, dizziness; *less commonly* dyspepsia, vomiting, abdominal pain, dry mouth, drowsiness, rash (rarely Stevens-Johnson syndrome, toxic epidermal necrolysis); *rarely* paralytic ileus, fatigue, hypertonia, urinary retention

Licensed use **capsules** not licensed for use in children under 8 years; **syrup** not licensed for use in children under 4 years; not licensed for use in children for chronic diarrhoea

Indications and dose

Chronic diarrhoea

• By mouth

Child 1 month–1 year 100–200 micrograms/kg twice daily, 30 minutes before feeds; up to 2 mg/kg daily in divided doses occasionally required

Child 1–12 years 100–200 micrograms/kg (max. 2 mg) 3–4 times daily; up to 1.25 mg/kg daily in divided doses may be required (max. 16 mg daily)

Child 12–18 years 2–4 mg 2–4 times daily (max. 16 mg daily)

Acute diarrhoea (but see notes above)

• By mouth

Child 4–8 years 1 mg 3–4 times daily for *up to* 3 days only

Child 8–12 years 2 mg 4 times daily for up to 5 days

Child 12–18 years initially 4 mg, then 2 mg after each loose stool for up to 5 days (usual dose 6–8 mg daily; max. 16 mg daily)

Loperamide (Non-proprietary) **[POM]**

Capsules, loperamide hydrochloride 2 mg, net price 30-cap pack = £1.74

Tablets, loperamide hydrochloride 2 mg, net price 30-tab pack = £2.15

Brands include *Norimode*®

Note Loperamide can be sold to the public, for use in children over 12 years, provided it is licensed and labelled for the treatment of acute diarrhoea

Imodium® (Janssen) **[POM]**

Syrup, sugar-free, red, loperamide hydrochloride 1 mg/5 mL. Net price 100 mL = £1.17

Compound preparations**Imodium® Plus** (McNeil)

Caplets (= tablets), loperamide hydrochloride 2 mg, simeticone 125 mg, net price 6-tab pack = £2.27, 12-tab pack = £3.58

Dose**Acute diarrhoea with abdominal colic**

Child 12–18 years initially 1 caplet, then 1 caplet after each loose stool; max. 4 caplets daily for up to 2 days

1.4.3 Enkephalinase inhibitors

Racecadotril is a pro-drug of thiorphan. Thiorphan is an enkephalinase inhibitor that inhibits the breakdown of endogenous opioids, thereby reducing intestinal secretions. Racecadotril is licensed, as an adjunct to rehydration, for the symptomatic treatment of uncomplicated acute diarrhoea; it should only be used in children over 3 months of age when usual supportive measures, including oral rehydration, are insufficient to control the condition. Racecadotril does not affect the duration of intestinal transit.

The *Scottish Medicines Consortium*, p. 3 has advised (November 2012) that racecadotril (*Hidrasec*®) is **not** recommended for use within NHS Scotland for the treatment of acute diarrhoea because there is insufficient evidence that it improves the recovery rate.

RACECADOTRIL

Hepatic impairment manufacturer advises avoid

Renal impairment manufacturer advises avoid

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects headache; *less commonly* rash

Indications and dose

Acute uncomplicated diarrhoea (but see notes above)

- **By mouth**

Child 3 months–18 years

Body-weight less than 9 kg 10 mg 3 times daily until diarrhoea stops (max. duration of treatment 7 days)

Body-weight 9–13 kg 20 mg 3 times daily until diarrhoea stops (max. duration of treatment 7 days)

Body-weight 13–27 kg 30 mg 3 times daily until diarrhoea stops (max. duration of treatment 7 days)

Body-weight over 27 kg 60 mg 3 times daily until diarrhoea stops (max. duration of treatment 7 days)

Hidrasec® (Abbott Healthcare) (PoM)

Granules, racecadotril 10 mg/sachet, net price 20-sachet pack = £8.42; 30 mg/sachet, 20-sachet pack = £8.42. Counselling, administration

Excipients include sucrose 970 mg/10 mg sachet (2.9 g/30 mg sachet)

Administration granules may be added to food or mixed with water or bottle feeds and then taken immediately

1.5 Chronic bowel disorders**1.5.1 Aminosalicylates****1.5.2 Corticosteroids****1.5.3 Drugs affecting the immune response****1.5.4 Food allergy**

Individual symptoms of chronic bowel disorders need specific treatment including dietary manipulation as well as drug treatment and the maintenance of a liberal fluid intake.

Inflammatory bowel disease

Chronic inflammatory bowel diseases include *ulcerative colitis* and *Crohn's disease*. The treatment of inflammatory bowel disease in children should be initiated and supervised by a paediatric gastroenterologist. Effective management requires drug therapy, attention to nutrition, and in severe or chronic active disease, surgery.

Aminosalicylates (balsalazide, mesalazine, olsalazine, and sulfasalazine), **corticosteroids** (hydrocortisone, budesonide, and prednisolone), and **drugs that affect the immune response** are used in the treatment of inflammatory bowel disease.

Treatment of acute ulcerative colitis and Crohn's disease

Acute mild to moderate disease affecting the rectum (proctitis) or the recto-sigmoid (distal colitis) is treated initially with local application of an aminosalicylate (section 1.5.1); alternatively a local corticosteroid (section 1.5.2) can be used but it is less effective. Foam preparations and suppositories are useful for children who have difficulty retaining liquid enemas.

Diffuse inflammatory bowel disease or disease that does not respond to local therapy requires oral treatment. Mild disease affecting the proximal colon can be treated with an oral aminosalicylate alone; a combination of a local and an oral aminosalicylate can be used in proctitis or distal colitis. Refractory or moderate inflammatory bowel disease usually requires adjunctive use of an oral corticosteroid such as **prednisolone** (section 1.5.2) for 4–8 weeks. Modified-release **budesonide** is used for children with Crohn's disease affecting the ileum and the ascending colon; it causes fewer systemic side-effects than oral prednisolone, but may be less effective. As an alternative to an oral corticosteroid, **enteral nutrition** (Appendix 2) may be used for 6–8 weeks in children with active Crohn's disease.

Severe inflammatory bowel disease or disease that is not responding to an oral corticosteroid requires hospital admission and treatment with an intravenous corticosteroid such as **hydrocortisone** (p. 381) or **methylprednisolone** (p. 382); other therapy may include intravenous fluid and electrolyte replacement, and possibly parenteral nutrition. Children with ulcerative colitis that fails to respond adequately to these measures may benefit from a short course of ciclosporin. Children with unresponsive or chronically active Crohn's disease may benefit from azathioprine, mercaptopurine, or once-weekly methotrexate; these drugs have a slow onset of action.

Infliximab (section 1.5.3) is used in specialist centres for children with severe active Crohn's disease or severe active ulcerative colitis whose condition has not responded adequately to treatment with a corticosteroid

and a conventional drug that affects the immune response, or who are intolerant of them. The *Scottish Medicines Consortium* (p. 3) has advised (February 2013) that infliximab (*Remicade*®) is accepted for restricted use within NHS Scotland, as an alternative to ciclosporin, for severe active ulcerative colitis in children aged 6–18 years. **Adalimumab** (section 1.5.3) is licensed for children with severe active Crohn's disease whose condition has not responded adequately to conventional therapy (including corticosteroids, other drugs that affect the immune response, and primary nutrition therapy) or who are intolerant of it. There are concerns about the long-term safety of infliximab and adalimumab in children; hepatosplenic T-cell lymphoma has been reported.

Crohn's disease of the mouth or of the perineum is more common in children than in adults and it is difficult to treat; elimination diets and the use of a topical corticosteroid (section 13.4) may be beneficial, but a systemic corticosteroid (section 6.3.2) and occasionally azathioprine may be required in severe cases.

NICE guidance

Infliximab for Crohn's disease (May 2010)

In children over 6 years of age, infliximab is recommended for the treatment of severe active Crohn's disease that has not responded to conventional therapy (including corticosteroids, other drugs affecting the immune response, and primary nutrition therapy) or when conventional therapy cannot be used because of intolerance or contra-indications. Infliximab should be given as a planned course of treatment for 12 months or until treatment failure, whichever is shorter. Treatment should be continued beyond 12 months only if there is evidence of active disease—in these cases the need for treatment should be reviewed at least annually. If the disease relapses after stopping treatment, infliximab can be restarted [but see Hypersensitivity Reactions under Infliximab, p. 55].

www.nice.org.uk/TA187

NICE guidance

Infliximab for subacute manifestations of ulcerative colitis (April 2008)

Infliximab is **not** recommended for the treatment of subacute manifestations of moderate to severe active ulcerative colitis that would normally be managed in an outpatient setting.

www.nice.org.uk/TA140

Maintenance of remission of acute ulcerative colitis and Crohn's disease

Children should be advised not to smoke because smoking increases the risk of relapse in Crohn's disease. Smoking cessation (section 4.10.2) should be encouraged when necessary. **Aminosalicylates** are efficacious in the maintenance of remission of ulcerative colitis, but there is no evidence of efficacy in the maintenance of remission of Crohn's disease. Corticosteroids are **not** suitable for maintenance treatment because of their side-effects. In resistant or frequently relapsing cases either **azathioprine** (section 1.5.3) or **mercaptopurine** (section 1.5.3) may be helpful. **Methotrexate** (section 1.5.3) is used in Crohn's disease when azathioprine or mercaptopurine are ineffective or not tolerated. **Infliximab** (p. 55) can be used for maintenance therapy in Crohn's disease or

ulcerative colitis in children who respond to the initial induction course of this drug. **Adalimumab** (p. 55) is also licensed for maintenance therapy in Crohn's disease. There are concerns about the long-term safety of infliximab and adalimumab in children.

Fistulating Crohn's disease Treatment may not be necessary for simple, asymptomatic perianal fistulas. **Metronidazole** (section 5.1.11) or **ciprofloxacin** (section 5.1.12) may be beneficial for the treatment of fistulating Crohn's disease [both unlicensed for this indication]. Metronidazole by mouth is used at a dose of 7.5 mg/kg 3 times daily, usually for 1 month; it should not be used for longer than 3 months because of concerns about peripheral neuropathy. Ciprofloxacin by mouth is given at a dose of 5 mg/kg twice daily. Other antibacterials should be given if specifically indicated (e.g. sepsis associated with fistulas and perianal disease) and for managing bacterial overgrowth in the small bowel. Fistulas may also require surgical exploration and local drainage.

Either **azathioprine** or **mercaptopurine** is used as a second-line treatment for fistulating Crohn's disease and continued for maintenance. **Infliximab** is used for fistulating Crohn's disease refractory to conventional treatments; maintenance therapy with infliximab should be considered for patients who respond to the initial induction course.

Adjunctive treatment of inflammatory bowel disease Due attention should be paid to diet; high-fibre or low-residue diets should be used as appropriate.

Antimotility drugs such as codeine phosphate and loperamide, and antispasmodic drugs may precipitate paralytic ileus and megacolon in active ulcerative colitis; treatment of the inflammation is more logical. Laxatives may be required in proctitis. Diarrhoea resulting from the loss of bile-salt absorption (e.g. in terminal ileal disease or bowel resection) may improve with **colestyramine** (section 1.9.2), which binds bile salts.

Irritable bowel syndrome

Irritable bowel syndrome can present with pain, constipation, or diarrhoea. Some children have important psychological aggravating factors which respond to reassurance. The **fibre** intake of children with irritable bowel syndrome should be reviewed. If an increase in dietary fibre is required, soluble fibre (e.g. oats, ispaghula husk, or sterculia) is recommended; insoluble fibre (e.g. bran) should be avoided. A **laxative** (section 1.6) can be used to treat constipation. An osmotic laxative, such as a macrogol, is preferred; lactulose may cause bloating. **Loperamide** (section 1.4.2) may relieve diarrhoea and antispasmodic drugs (section 1.2) may relieve pain. Opioids with a central action, such as codeine, are better avoided because of the risk of dependence.

Clostridium difficile infection

Clostridium difficile infection is caused by colonisation of the colon with *Clostridium difficile* and production of toxin. It often follows antibiotic therapy and is usually of acute onset, but may become chronic. It is a particular hazard of ampicillin, amoxicillin, co-amoxiclav, second- and third-generation cephalosporins, clindamycin, and quinolones, but few antibacterials are free of this side-effect. Oral **metronidazole** (section 5.1.11) or oral **vancomycin** (section 5.1.7) are used as specific

treatment; vancomycin may be preferred for very sick patients. Metronidazole can be given by intravenous infusion if oral treatment is inappropriate.

Malabsorption syndromes

Individual conditions need specific management and also general nutritional consideration. Coeliac disease (gluten enteropathy) usually needs a gluten-free diet (Appendix 2) and pancreatic insufficiency needs pancreatic supplements (section 1.9.4).

For further information on foods for special diets (ACBS), see Appendix 2.

1.5.1 Aminosaliclates

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

Cautions Renal function should be monitored before starting an oral aminosaliclate, at 3 months of treatment, and then annually during treatment (more frequently in renal impairment). Blood disorders can occur with aminosaliclates (see recommendation below).

Blood disorders

Children receiving aminosaliclates and their carers should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment. A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

Contra-indications Aminosaliclates should be avoided in salicylate hypersensitivity.

Side-effects Side-effects of the aminosaliclates include diarrhoea, nausea, vomiting, abdominal pain, exacerbation of symptoms of colitis, headache, hypersensitivity reactions (including rash and urticaria); side-effects that occur rarely include acute pancreatitis, hepatitis, myocarditis, pericarditis, lung disorders (including eosinophilia and fibrosing alveolitis), peripheral neuropathy, blood disorders (including agranulocytosis, aplastic anaemia, leucopenia, methaemoglobinemia, neutropenia, and thrombocytopenia—see also recommendation above), renal dysfunction (interstitial nephritis, nephrotic syndrome), myalgia, arthralgia, skin reactions (including lupus erythematosus-like syndrome, Stevens-Johnson syndrome), alopecia.

BALSALAZIDE SODIUM

Cautions see notes above; also history of asthma; **interactions:** Appendix 1 (aminosalicylates)

Blood disorders see recommendation above

Contra-indications see notes above

Hepatic impairment avoid in severe impairment

Renal impairment manufacturer advises avoid in moderate to severe impairment

Pregnancy manufacturer advises avoid

Breast-feeding monitor infant for diarrhoea

Side-effects see notes above; also cholelithiasis

Licensed use not licensed for use in children under 18 years

Indications and dose

Treatment of mild to moderate ulcerative colitis and maintenance of remission

• By mouth

Child 12–18 years acute attack, 2.25 g 3 times daily until remission occurs or for up to max. 12 weeks; maintenance, 1.5 g twice daily, adjusted according to response (max. 3 g twice daily)

Colazide® (Almirall) (PoM)

Capsules, beige, balsalazide sodium 750 mg, net price 130-cap pack = £30.42. Label: 21, 25, counselling, blood disorder symptoms (see recommendation above)

MESALAZINE

Cautions see notes above; **interactions:** Appendix 1 (aminosalicylates)

Blood disorders see recommendation above

Contra-indications see notes above; blood clotting abnormalities

Hepatic impairment avoid in severe impairment

Renal impairment use with caution; avoid if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Pregnancy negligible quantity crosses placenta

Breast-feeding diarrhoea reported but negligible amounts detected in breast milk; monitor infant for diarrhoea

Side-effects see notes above

Licensed use *Asacol®* (all preparations) and *Salofalk®* enema not licensed for use in children under 18 years; *Salofalk®* suppositories, *Pentasa®* tablets and suppositories not licensed for use in children under 15 years; *Pentasa®* granules and *Salofalk®* tablets and granules not licensed for use in children under 6 years; *Salofalk®* rectal foam no dose recommendations for children (age range not specified by manufacturer)

Indications and dose

Treatment of mild to moderate ulcerative colitis and maintenance of remission for dose see under preparations below

There is no evidence to show that any one oral preparation of mesalazine is more effective than another; however, the delivery characteristics of oral mesalazine preparations may vary. If it is necessary to switch a patient to a different brand of mesalazine, the patient and carers should be advised to report any changes in symptoms

Asacol® (Warner Chilcott) (PoM)

Foam enema, mesalazine 1 g/metered application, net price 14-application canister with disposable

applicators and plastic bags = £26.72. Counselling, blood disorder symptoms (see recommendation above)

Excipients include disodium edetate, hydroxybenzoates (parabens), polysorbate 20, sodium metabisulfite
Dose

Acute attack affecting the rectosigmoid region

- By rectum

Child 12–18 years 1 metered application (mesalazine 1 g) into the rectum daily for 4–6 weeks

Acute attack affecting the descending colon

- By rectum

Child 12–18 years 2 metered applications (mesalazine 2 g) once daily for 4–6 weeks

Suppositories, mesalazine 250 mg, net price 20-suppos pack = £4.82; 500 mg, 10-suppos pack = £4.82. Counselling, blood disorder symptoms (see recommendation above)

Dose

Treatment and maintenance of remission of ulcerative colitis affecting the rectosigmoid region

- By rectum

Child 12–18 years 250–500 mg 3 times daily, with last dose at bedtime

Asacol® MR (Warner Chilcott) (PoM)

Tablets, red, e/c, mesalazine 400 mg, net price 90-tab pack = £29.41, 120-tab pack = £39.21. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose

Acute attack

- By mouth

Child 12–18 years 800 mg 3 times daily

Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis

- By mouth

Child 12–18 years 400–800 mg 2–3 times daily

Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine

Ipcocol® (Sandoz) (PoM)

Tablets, e/c, mesalazine 400 mg, net price 120-tab pack = £17.68. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose

Acute attack

- By mouth

Child 6–18 years and body-weight over 40 kg 800 mg 3 times daily

Maintenance of remission

- By mouth

Child 6–18 years and body-weight over 40 kg 1.2–2 g daily in divided doses

Octasa® (Tillotts) (PoM)

Tablets, m/r, red-brown, e/c, mesalazine 400 mg, net price 90-tab pack = £19.50, 120-tab pack = £26.00; 800 mg, 90-tab pack = £47.50, 180-tab pack = £95.00. Label: 25, counselling, blood disorder symptoms (see recommendation above)

Dose

Acute attack

- By mouth

Child 6–18 years and body-weight over 40 kg 2.4–4 g daily in divided doses

Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis

- By mouth

Child 6–18 years and body-weight over 40 kg 1.2–2 g once daily or in divided doses

Pentasa® (Ferring) (PoM)

Tablets, m/r, mesalazine 500 mg (grey, scored), net price 100-tab pack = £30.74; 1 g, 60-tab pack = £36.89. Counselling, administration (see dose), blood disorder symptoms (see recommendation above)

Dose

Acute attack

- By mouth

Child 5–18 years

Body-weight under 40 kg 10–20 mg/kg 3 times daily

Body-weight over 40 kg 1–2 g twice daily; total daily dose may alternatively be given in 3 divided doses

Maintenance of remission

- By mouth

Child 5–18 years

Body-weight under 40 kg 7.5–15 mg/kg twice daily; total daily dose may alternatively be given in 3 divided doses

Body-weight over 40 kg 2 g once daily

Administration tablets may be halved, quartered, or dispersed in water, but should not be chewed

Granules, m/r, pale grey-brown, mesalazine 1 g/sachet, net price 50-sachet pack = £30.74; 2 g/sachet, 60-sachet pack = £73.78. Counselling, administration (see dose), blood disorder symptoms (see recommendation above)

Dose

Acute attack

- By mouth

Child 5–18 years

Body-weight under 40 kg 10–20 mg/kg 3 times daily

Body-weight over 40 kg 1–2 g twice daily; total daily dose may alternatively be given in 3 or 4 divided doses

Maintenance of remission

- By mouth

Child 5–18 years

Body-weight under 40 kg 7.5–15 mg/kg twice daily; total daily dose may alternatively be given in 3 divided doses

Body-weight over 40 kg 2 g once daily

Administration contents of one sachet should be weighed and divided immediately before use; discard any remaining granules. Granules should be placed on tongue and washed down with water or orange juice without chewing

Retention enema, mesalazine 1 g in 100-mL pack, net price 7 enemas = £17.73. Counselling, blood disorder symptoms (see recommendation above)

Dose

Acute attack affecting the rectosigmoid region

- By rectum

Child 12–18 years 1 g at bedtime

Suppositories, mesalazine 1 g, net price 28-suppos pack = £40.01. Counselling, blood disorder symptoms (see recommendation above)

Dose

Acute attack, ulcerative proctitis

- By rectum

Child 12–18 years 1 g daily for 2–4 weeks

Maintenance, ulcerative proctitis

- By rectum

Child 12–18 years 1 g daily

Salofalk® (Dr Falk) (PoM)

Tablets, e/c, yellow, mesalazine 250 mg, net price 100-tab pack = £16.19; 500 mg, 100-tab pack = £32.38. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose**Acute attack**

- By mouth

Child 5–18 years

Body-weight under 40 kg 10–20 mg/kg 3 times daily

Body-weight over 40 kg 0.5–1 g 3 times daily

Maintenance of remission

- By mouth

Child 5–18 years

Body-weight under 40 kg 7.5–15 mg/kg twice daily; total daily dose may alternatively be given in 3 divided doses

Body-weight over 40 kg 500 mg 3 times daily

Granules, m/r, grey, e/c, vanilla-flavoured, mesalazine 500 mg/sachet, net price 100-sachet pack = £28.74; 1 g/sachet, 50-sachet pack = £28.74; 1.5 g/sachet, 60-sachet pack = £48.85; 3 g/sachet, 60-sachet pack = £97.70. Label: 25, counselling, administration (see dose), blood disorder symptoms (see recommendation above)

Excipients include aspartame (section 9.4.1)

Dose**Acute attack**

- By mouth

Child 5–18 years

Body-weight under 40 kg 30–50 mg/kg once daily (preferably in the morning) or 10–20 mg/kg 3 times daily

Body-weight over 40 kg 1.5–3 g once daily (preferably in the morning) or 0.5–1 g 3 times daily

Maintenance of remission

- By mouth

Child 5–18 years

Body-weight under 40 kg 7.5–15 mg/kg twice daily; total daily dose may alternatively be given in 3 divided doses

Body-weight over 40 kg 500 mg 3 times daily

Administration Granules should be placed on the tongue and washed down with water without chewing

Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine

Suppositories, mesalazine 500 mg. Net price 30-sup-pose pack = £14.81. Counselling, blood disorder symptoms (see recommendation above)

Dose**Acute attack**

- By rectum

Child 12–18 years 0.5–1 g 2–3 times daily adjusted according to response

Enema, mesalazine 2 g in 59-mL pack. Net price 7 enemas = £29.92. Counselling, blood disorder symptoms (see recommendation above)

Dose**Acute attack or maintenance**

- By rectum

Child 12–18 years 2 g once daily at bedtime

Rectal foam, mesalazine 1 g/metered application, net price 14-application canister with disposable applicators and plastic bags = £30.17. Counselling,

blood disorder symptoms (see recommendation above)

Excipients include cetostearyl alcohol, disodium edetate, polysorbate 60, propylene glycol, sodium metabisulfite

Dose**Mild ulcerative colitis affecting sigmoid colon and rectum**

- By rectum

Child 12–18 years 2 metered applications (mesalazine 2 g) into the rectum at bedtime or in 2 divided doses

OLSALAZINE SODIUM

Cautions see notes above; **interactions:** Appendix 1 (aminosalicylates)

Blood disorders see recommendation above

Contra-indications see notes above

Renal impairment use with caution; manufacturer advises avoid in significant impairment

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk

Breast-feeding monitor infant for diarrhoea

Side-effects see notes above; watery diarrhoea common; also reported, tachycardia, palpitation, pyrexia, blurred vision, and photosensitivity

Licensed use not licensed for use in children under 12 years

Indications and dose**Treatment of acute attack of mild ulcerative colitis**

- By mouth

Child 2–18 years 500 mg twice daily after food increased if necessary over 1 week to max. 1 g 3 times daily

Maintenance of remission of mild ulcerative colitis

- By mouth

Child 2–18 years 250–500 mg twice daily after food

Administration Capsules can be opened and contents sprinkled on food

Dipentum® (UCB Pharma) (PoM)

Capsules, brown, olsalazine sodium 250 mg. Net price 112-cap pack = £19.77. Label: 21, counselling, blood disorder symptoms (see recommendation above)

Tablets, yellow, scored, olsalazine sodium 500 mg. Net price 60-tab pack = £21.18. Label: 21, counselling, blood disorder symptoms (see recommendation above)

SULFASALAZINE

(Sulphasalazine)

Cautions see notes above; also history of allergy or asthma; G6PD deficiency (section 9.1.5); slow acetylator status; risk of haematological and hepatic toxicity (differential white cell, red cell, and platelet counts initially and at monthly intervals for first 3 months; liver function tests at monthly intervals for first 3 months); maintain adequate fluid intake; upper gastro-intestinal side-effects common with doses over 4 g daily; acute porphyria (section 9.8.2); **interactions:** Appendix 1 (aminosalicylates)

Blood disorders see recommendation above

Contra-indications see notes above; also sulfonamide hypersensitivity; child under 2 years of age

Hepatic impairment use with caution

Renal impairment risk of toxicity, including crystalluria, in moderate impairment—ensure high fluid intake; avoid in severe impairment

Pregnancy theoretical risk of neonatal haemolysis in third trimester; adequate folate supplements should be given to mother

Breast-feeding small amount in milk (1 report of bloody diarrhoea); theoretical risk of neonatal haemolysis especially in G6PD-deficient infants

Side-effects see notes above; also cough, insomnia, dizziness, fever, blood disorders (including Heinz body anaemia, megaloblastic anaemia), proteinuria, tinnitus, stomatitis, taste disturbances, and pruritus; *less commonly* dyspnoea, depression, convulsions, vasculitis, and alopecia; also reported loss of appetite, hypersensitivity reactions (including exfoliative dermatitis, epidermal necrolysis, photosensitivity, anaphylaxis, serum sickness), ataxia, hallucinations, aseptic meningitis, oligospermia, crystalluria, disturbances of smell, and parotitis; yellow-orange discoloration of skin, urine, and other body fluids; some soft contact lenses may be stained

Indications and dose

Treatment of acute attack of mild to moderate and severe ulcerative colitis, active Crohn's disease

- By mouth

Child 2–12 years 10–15 mg/kg (max. 1 g) 4–6 times daily until remission occurs; increased to max. 60 mg/kg daily in divided doses, if necessary

Child 12–18 years 1–2 g 4 times daily until remission occurs

Maintenance of remission of mild to moderate and severe ulcerative colitis

- By mouth

Child 2–12 years 5–7.5 mg/kg (max. 500 mg) 4 times daily

Child 12–18 years 500 mg 4 times daily

Treatment of mild to moderate or severe ulcerative colitis and maintenance of remission, active Crohn's disease

- By rectum as suppositories

Child 5–8 years 500 mg twice daily

Child 8–12 years 500 mg in the morning and 1 g at night

Child 12–18 years 0.5–1 g twice daily

Juvenile idiopathic arthritis section 10.1.3

Sulfasalazine (Non-proprietary) (PoM)

Tablets, sulfasalazine 500 mg, net price 112 = £5.58. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

Tablets, e/c, sulfasalazine 500 mg. Net price 112-tab pack = £7.67. Label: 5, 14, 25, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

Brands include *Sulazine EC*[®]

Suspension, sulfasalazine 250 mg/5 mL, net price 500 mL = £39.75. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

Excipients may include alcohol

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Salazopyrin[®] (Pharmacia) (PoM)

Tablets, yellow, scored, sulfasalazine 500 mg. Net price 112-tab pack = £6.97. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

EN-Tabs[®] (= tablets e/c), yellow, f/c, sulfasalazine 500 mg. Net price 112-tab pack = £8.43. Label: 5, 14, 25, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

Suppositories, yellow, sulfasalazine 500 mg. Net price 10 = £3.30. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

1.5.2 Corticosteroids

For the role of corticosteroids in acute ulcerative colitis and Crohn's disease, see Inflammatory Bowel Disease, p. 47.

BUDESONIDE

Cautions section 6.3.2; **interactions**: Appendix 1 (corticosteroids)

Contra-indications section 6.3.2

Hepatic impairment section 6.3.2

Pregnancy section 6.3.2

Breast-feeding section 6.3.2

Side-effects section 6.3.2

Licensed use not licensed for use in children

Indications and dose

See preparations

Administration Capsules can be opened and the contents mixed with apple or orange juice

Budenofalk[®] (Dr Falk) (PoM)

Capsules, pink, enclosing e/c granules, budesonide 3 mg, net price 100-cap pack = £75.05. Label: 5, 10, steroid card, 22, 25

Dose

Mild to moderate Crohn's disease affecting ileum or ascending colon, chronic diarrhoea due to collagenous colitis

- By mouth

Child 12–18 years 3 mg 3 times daily for up to 8 weeks; reduce dose for the last 2 weeks of treatment. See also section 6.3.2

Entocort[®] (AstraZeneca) (PoM)

CR Capsules, grey/pink, enclosing e/c, m/r granules, budesonide 3 mg, net price 100-cap pack = £99.00. Label: 5, 10, steroid card, 22, 25

Note Dispense in original container (contains desiccant)

Dose

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

- By mouth

Child 12–18 years 9 mg once daily in the morning before breakfast for up to 8 weeks; reduce dose for the last 2–4 weeks of treatment. See also section 6.3.2

Enema, budesonide 2 mg/100 mL when dispersible tablet reconstituted in isotonic saline vehicle, net

price pack of 7 dispersible tablets and bottles of vehicle = £39.60

Dose

Ulcerative colitis involving rectal and recto-sigmoid disease

- By rectum

Child 12–18 years 1 enema at bedtime for 4 weeks

HYDROCORTISONE

Cautions section 6.3.2; systemic absorption may occur; prolonged use should be avoided

Contra-indications intestinal obstruction, bowel perforation, recent intestinal anastomoses, extensive fistulas; untreated infection

Side-effects section 6.3.2; also local irritation

Indications and dose

Inflammatory bowel disease

- By intravenous administration
See p. 381
- By rectum
See preparations

Colifoam® (Meda) (PoM)

Foam in aerosol pack, hydrocortisone acetate 10%, net price 14-application cannister with applicator = £9.33

Excipients include cetyl alcohol, hydroxybenzoates (parabens), propylene glycol

Dose

Ulcerative colitis, proctitis, proctosigmoiditis

- By rectum

Child 2–18 years initially 1 metered application (125 mg hydrocortisone acetate) inserted into the rectum once or twice daily for 2–3 weeks, then once on alternate days

PREDNISOLONE

Cautions section 6.3.2; systemic absorption may occur; prolonged use should be avoided

Contra-indications section 6.3.2; intestinal obstruction, bowel perforation, recent intestinal anastomoses, extensive fistulas; untreated infection

Hepatic impairment section 6.3.2

Renal impairment section 6.3.2

Pregnancy section 6.3.2

Breast-feeding section 6.3.2

Side-effects section 6.3.2

Licensed use prednisolone rectal foam not licensed for use in children (age range not specified by manufacturer)

Indications and dose

Ulcerative colitis, Crohn's disease see also under preparations, below

- By mouth

Child 2–18 years 2 mg/kg (max. 60 mg) once daily until remission occurs, followed by reducing doses

- By rectum

See under preparations

Other indications section 6.3.2

Oral preparations

Section 6.3.2

Rectal preparations

Prednisolone (Non-proprietary) (PoM)

Rectal foam in aerosol pack, prednisolone 20 mg (as metasulfobenzonate sodium)/metered application, net price 14-application cannister with disposable applicators = £68.00

Dose

Proctitis and distal ulcerative colitis

- By rectum

Child 12–18 years 1 metered application (20 mg prednisolone) inserted into the rectum once or twice daily for 2 weeks, continued for further 2 weeks if good response

Predsol® (RPH) (PoM)

Suppositories, prednisolone 5 mg (as sodium phosphate). Net price 10 = £1.35

Dose

Proctitis and rectal complications of Crohn's disease

- By rectum

Child 2–18 years 5 mg inserted night and morning after a bowel movement

1.5.3 Drugs affecting the immune response

Azathioprine, mercaptopurine, or once weekly **methotrexate** are used to induce remission in unresponsive or chronically active Crohn's disease. Azathioprine or mercaptopurine may also be helpful for retaining remission in frequently relapsing inflammatory bowel disease; once weekly methotrexate is used in Crohn's disease when azathioprine or mercaptopurine are ineffective or not tolerated. Response to azathioprine or mercaptopurine may not become apparent for several months. Folic acid (section 9.1.2) should be given to reduce the possibility of methotrexate toxicity. Folic acid is usually given at a dose of 5 mg weekly on a different day to the methotrexate; alternative regimens may be used in some settings.

Ciclosporin (cyclosporin) is a potent immunosuppressant and is markedly nephrotoxic. In children with severe ulcerative colitis unresponsive to other treatment, ciclosporin may reduce the need for urgent colorectal surgery.

AZATHIOPRINE

Cautions section 8.2.1; interactions: Appendix 1 (azathioprine)

Contra-indications section 8.2.1

Hepatic impairment section 8.2.1

Renal impairment section 8.2.1

Pregnancy section 8.2.1

Breast-feeding section 8.2.1

Side-effects section 8.2.1

Indications and dose

Severe ulcerative colitis and Crohn's disease

- By mouth

Child 2–18 years initially 2 mg/kg once daily, then increased if necessary up to 2.5 mg/kg once daily

Transplantation rejection section 8.2.1

Rheumatic diseases section 10.1.3

Preparations

Section 8.2.1

CICLOSPORIN

Cautions section 8.2.2; interactions: Appendix 1 (ciclosporin)

Hepatic impairment section 8.2.2

Renal impairment section 8.2.2

Pregnancy section 8.2.2

Breast-feeding section 8.2.2

Side-effects section 8.2.2

Licensed use not licensed for use in ulcerative colitis

Indications and dose**Refractory ulcerative colitis**

- By mouth

Child 2–18 years initially 2 mg/kg twice daily, dose adjusted according to blood-ciclosporin concentration and response; max. 5 mg/kg twice daily

Important For advice on counselling and conversion between preparations, see section 8.2.2

- By intravenous infusion

Child 3–18 years initially 0.5–1 mg/kg twice daily, dose adjusted according to blood-ciclosporin concentration and response

Nephrotic syndrome section 8.2.2

Transplantation rejection and auto-immune conditions section 8.2.2

Atopic dermatitis and psoriasis section 13.5.3

Administration for *intermittent intravenous infusion*, dilute to a concentration of 0.5–2.5 mg/mL with Glucose 5% or Sodium Chloride 0.9% and give over 2–6 hours; not to be used with PVC equipment; observe patient for signs of anaphylaxis for at least 30 minutes after starting infusion and at frequent intervals thereafter

Preparations

Section 8.2.2

MERCAPTOPURINE

(6-Mercaptopurine)

Cautions section 8.1.3; see also Azathioprine, section 8.2.1

Contra-indications section 8.1.3

Hepatic impairment section 8.1.3

Renal impairment section 8.1.3

Pregnancy section 8.1.3

Breast-feeding section 8.1.3

Side-effects section 8.1.3

Licensed use not licensed for use in severe ulcerative colitis and Crohn's disease; for other indications, see section 8.1.3

Indications and dose**Severe ulcerative colitis and Crohn's disease**

- By mouth

Child 2–18 years 1–1.5 mg/kg once daily (initial max. 50 mg; may be increased to 75 mg once daily)

Acute leukaemias section 8.1.3

Preparations

Section 8.1.3

METHOTREXATE

Cautions section 10.1.3

Contra-indications section 10.1.3

Hepatic impairment section 10.1.3

Renal impairment section 8.1.3

Pregnancy section 8.1.3

Breast-feeding section 8.1.3

Side-effects section 10.1.3

Licensed use not licensed for use in children for non-malignant conditions

Indications and dose**Severe acute Crohn's disease**

- By subcutaneous or intramuscular injection

Child 7–18 years 15 mg/m² (max. 25 mg) once weekly

Maintenance of remission of severe Crohn's disease

- By mouth or by subcutaneous or intramuscular injection

Child 7–18 years 15 mg/m² (max. 25 mg) once weekly; dose reduced according to response to lowest effective dose

Safe Practice

Note that the above dose is a **weekly** dose. To avoid error with low-dose methotrexate, it is recommended that:

- the child or their carer is carefully advised of the **dose** and **frequency** and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the child or their carer is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).

Malignant disease section 8.1.3

Rheumatic disease section 10.1.3

Psoriasis section 13.5.3

Preparations

Section 10.1.3

Cytokine modulators

Infliximab and **adalimumab** are monoclonal antibodies which inhibit the pro-inflammatory cytokine, tumour necrosis factor alpha. They are used in the treatment of severe refractory Crohn's disease. Infliximab is also used in the treatment of severe refractory ulcerative colitis. They should be used only when treatment with other immunomodulating drugs has failed or is not tolerated and for children in whom surgery is inappropriate. Cytokine modulators should be used under specialist supervision. Adequate resuscitation facilities must be available when infliximab is used.

ADALIMUMAB

Cautions section 10.1.3, p. 515

Important See section 10.1.3, p. 515 for information on tuberculosis and blood disorders

Contra-indications section 10.1.3, p. 515

Pregnancy section 10.1.3, p. 515

Breast-feeding section 10.1.3, p. 515

Side-effects section 10.1.3, p. 515

Indications and dose

Severe active Crohn's disease

- By subcutaneous injection

Child 6–18 years

Body-weight under 40 kg initially 40 mg, then 20 mg 2 weeks after initial dose *or* accelerated regimen, initially 80 mg, then 40 mg 2 weeks after initial dose; maintenance, 20 mg on alternate weeks, increased if necessary to 20 mg weekly; review treatment if no response within 12 weeks of initial dose

Body-weight over 40 kg initially 80 mg, then 40 mg 2 weeks after initial dose *or* accelerated regimen, initially 160 mg (alternatively can be given as divided injections over 2 days), then 80 mg 2 weeks after initial dose; maintenance, 40 mg on alternate weeks, increased if necessary to 40 mg weekly; review treatment if no response within 12 weeks of initial dose

Note Max. 40 mg administered at a single site

Rheumatic disease section 10.1.3

Preparations

Section 10.1.3

INFLIXIMAB

Cautions monitor for infections before, during, and for 6 months after treatment (see also Tuberculosis below); predisposition to infection; chronic hepatitis B—monitor for active infection; mild heart failure (discontinue if symptoms develop or worsen); demyelinating CNS disorders (risk of exacerbation); history or development of malignancy; history of prolonged immunosuppressant or PUVA treatment in patients with psoriasis; **interactions:** Appendix 1 (infliximab)

Tuberculosis Children should be evaluated for tuberculosis before treatment. Active tuberculosis should be treated with standard treatment (section 5.1.9) for at least 2 months before starting infliximab. Children who have previously received adequate treatment for tuberculosis can start infliximab but should be monitored every 3 months for possible recurrence. In those without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting infliximab. In children at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with infliximab. Children and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop

Blood disorders Children and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop

Hypersensitivity reactions Hypersensitivity reactions (including fever, chest pain, hypotension, hypertension, dyspnoea, transient visual loss, pruritus, urticaria, serum sickness-like reactions, angioedema, anaphylaxis) reported

during or within 1–2 hours after infusion (risk greatest during first or second infusion or in children who discontinue other immunosuppressants). All children should be observed carefully for 1–2 hours after infusion and resuscitation equipment should be available for immediate use. Prophylactic antipyretics, antihistamines, or hydrocortisone may be administered. Readministration not recommended after infliximab-free interval of more than 16 weeks—risk of delayed hypersensitivity reactions. Children and carers should be advised to keep Alert card with them at all times and seek medical advice if symptoms of delayed hypersensitivity develop

Contra-indications severe infections (see also under Cautions); moderate or severe heart failure

Pregnancy use only if essential; manufacturer advises adequate contraception during and for at least 6 months after last dose

Breast-feeding amount probably too small to be harmful

Side-effects see under Cytokine Modulators (section 10.1.3) and Cautions above; also constipation, diarrhoea, dyspepsia, gastro-intestinal haemorrhage, gastro-oesophageal reflux, flushing, hypotension, hypertension, palpitation, tachycardia, sleep disturbances, dizziness, paraesthesia, hypoaesthesia, arthralgia, myalgia, epistaxis, alopecia, rash, ecchymosis, hyperhidrosis, new onset or worsening psoriasis, dry skin; *less commonly* hepatitis, cholecystitis, intestinal perforation, pancreatitis, heart failure, arrhythmia, bradycardia, syncope, peripheral ischaemia, pleurisy, pulmonary oedema, amnesia, agitation, confusion, nervousness, neuropathy, seizures, vaginitis, eye disorders, bullous eruption, cheilitis, seborrhoea, impaired healing, rosacea, hyperkeratosis, abnormal skin pigmentation; *rarely* pericardial effusion, vasospasm, interstitial lung disease, leukaemia, lymphoma, demyelinating disorders, Stevens-Johnson Syndrome, toxic epidermal necrolysis; also reported hepatic failure

Licensed use not licensed for fistulating Crohn's disease in children

Indications and dose

Severe active Crohn's disease

- By intravenous infusion

Child 6–18 years initially 5 mg/kg, then 5 mg/kg 2 weeks and 6 weeks after initial dose, then 5 mg/kg every 8 weeks; interval between maintenance doses adjusted according to response; discontinue if no response within 10 weeks of initial dose

Fistulating Crohn's disease

- By intravenous infusion

Child 6–18 years initially 5 mg/kg, then 5 mg/kg 2 weeks and 6 weeks after initial dose, then if condition has responded, consult literature for guidance on further doses

Severe active ulcerative colitis

- By intravenous infusion

Child 6–18 years initially 5 mg/kg, then 5 mg/kg 2 weeks and 6 weeks after initial dose, then 5 mg/kg every 8 weeks; discontinue if no response within 8 weeks of initial dose

Administration for *intravenous infusion* reconstitute each 100-mg vial of powder with 10 mL Water for Injections; to dissolve, gently swirl vial without shaking; allow to stand for 5 minutes; dilute required dose with Sodium Chloride 0.9% to a final volume of

250 mL and give through a low protein-binding filter (1.2 micron or less) over at least 2 hours; start infusion within 3 hours of reconstitution

Remicade® (MSD) (PoM)

Intravenous infusion, powder for reconstitution, infliximab, net price 100-mg vial = £419.62. Label: 10, alert card, counselling, tuberculosis, blood disorders, and hypersensitivity reactions

1.5.4 Food allergy

Allergy with classical symptoms of vomiting, colic and diarrhoea caused by specific foods such as cow's milk should be managed by strict avoidance. The condition should be distinguished from symptoms of occasional food intolerance in children with irritable bowel syndrome. **Sodium cromoglicate** (sodium cromoglycate) may be helpful as an adjunct to dietary avoidance.

SODIUM CROMOGLICATE (Sodium cromoglycate)

Pregnancy not known to be harmful

Breast-feeding unlikely to be present in milk

Side-effects occasional nausea, rashes, and joint pain

Indications and dose

Food allergy (in conjunction with dietary restriction)

• By mouth

Child 2–14 years 100 mg 4 times daily before meals, dose may be increased after 2–3 weeks to a max. 40 mg/kg daily and then reduced according to response

Child 14–18 years 200 mg 4 times daily before meals, dose may be increased after 2–3 weeks to max. 40 mg/kg daily and then reduced according to response

Asthma section 3.3.1

Allergic conjunctivitis section 11.4.2

Allergic rhinitis section 12.2.1

Administration capsules may be swallowed whole or the contents dissolved in hot water and diluted with cold water before taking

Nalcrom® (Sanofi-Aventis) (PoM)

Capsules, sodium cromoglicate 100 mg. Net price 100-cap pack = £41.14. Label: 22, counselling, administration

1.6 Laxatives

1.6.1 Bulk-forming laxatives

1.6.2 Stimulant laxatives

1.6.3 Faecal softeners

1.6.4 Osmotic laxatives

1.6.5 Bowel cleansing preparations

1.6.6 Peripheral opioid-receptor antagonists

1.6.7 Other drugs used in constipation

Laxatives should be prescribed by a healthcare professional experienced in the management of constipation in children. Delays of greater than 3 days between stools may increase the likelihood of pain on passing hard stools leading to anal fissure, anal spasm and eventually to a learned response to avoid defaecation.

In *infants*, increased intake of fluids, particularly fruit juice containing sorbitol (e.g. prune, pear, or apple), may be sufficient to soften the stool. In infants under 1 year of age with mild constipation, **lactulose** (section 1.6.4) can be used to soften the stool; either an oral preparation containing **macrogols** or, rarely, **glycerol** suppositories can be used to clear faecal impaction. The infant should be referred to a hospital paediatric specialist if these measures fail.

The diet of *children over 1 year of age* should be reviewed to ensure that it includes an adequate intake of fibre and fluid. An osmotic laxative containing **macrogols** (section 1.6.4) can also be used, particularly in children with chronic constipation; **lactulose** is an alternative in children who cannot tolerate a macrogol. If there is an inadequate response to the osmotic laxative, a **stimulant laxative** (section 1.6.2) can be added.

Treatment of faecal impaction may initially increase symptoms of soiling and abdominal pain. In children over 1 year of age with faecal impaction, an oral preparation containing **macrogols** (section 1.6.4) is used to clear faecal mass and to establish and maintain soft well-formed stools. If disimpaction does not occur after 2 weeks, a **stimulant laxative** (section 1.6.2) can be added. If the impacted mass is not expelled following treatment with macrogols and a stimulant laxative, a **sodium citrate** enema can be administered. Although rectal administration of laxatives may be effective, this route is frequently distressing for the child and may lead to persistence of withholding. A **phosphate enema** may be administered under specialist supervision if disimpaction does not occur after a sodium citrate enema; a **bowel cleansing preparation** (section 1.6.5) is an alternative. Manual evacuation under anaesthetic may be necessary if disimpaction does not occur after oral and rectal treatment, or if the child is afraid.

Long-term regular use of laxatives is essential to maintain well-formed stools and prevent recurrence in children with chronic constipation or a history of faecal impaction; intermittent use may provoke relapses. In children with chronic constipation, laxatives should be continued for several weeks after a regular pattern of bowel movements or toilet training is established. The dose of laxatives should then be tapered gradually, over a period of months, according to response. Some children may require laxative therapy for several years.

For children with chronic constipation, it may be necessary to exceed the licensed doses of some laxatives. Parents and carers of children should be advised to adjust the dose of laxative in order to establish a regular pattern of bowel movements in which stools are soft, well-formed, and passed without discomfort.

Laxatives should be administered at a time that produces an effect that is likely to fit in with the child's toilet routine.

Before prescribing laxatives it is important to be sure that the child is constipated and that the constipation is not secondary to an underlying undiagnosed complaint.

For the role of laxatives in the treatment of irritable bowel syndrome, see p. 48. For the prevention of opioid-induced constipation in palliative care, see p. 18.

Pregnancy If dietary and lifestyle changes fail to control constipation in pregnancy, moderate doses of poorly absorbed laxatives may be used. A bulk-forming laxative should be tried first. An osmotic laxative, such as lactulose, can also be used. Bisacodyl or senna may be suitable, if a stimulant effect is necessary.

Laxatives are also of value in *drug-induced constipation* (see Prescribing in Palliative Care, p. 18), in *distal intestinal obstruction syndrome* in children with cystic fibrosis, for the expulsion of *parasites* after anthelmintic treatment, and to clear the alimentary tract before *surgery and radiological procedures* (section 1.6.5).

The laxatives that follow have been divided into 5 main groups (sections 1.6.1–1.6.5). This simple classification disguises the fact that some laxatives have a complex action.

1.6.1 Bulk-forming laxatives

Bulk-forming laxatives are of value if the diet is deficient in fibre. They relieve constipation by increasing faecal mass which stimulates peristalsis; children and their carers should be advised that the full effect may take some days to develop.

During treatment with bulk-forming laxatives, adequate fluid intake must be maintained to avoid intestinal obstruction. Proprietary preparations containing a bulk-forming agent such as ispaghula husk are often difficult to administer to children.

Bulk-forming laxatives may be used in the management of children with *haemorrhoids*, *anal fissure*, and *irritable bowel syndrome*.

ISPAGHULA HUSK

Cautions adequate fluid intake should be maintained to avoid intestinal obstruction

Contra-indications difficulty in swallowing, intestinal obstruction, colonic atony, faecal impaction

Side-effects flatulence and abdominal distension (especially during the first few days of treatment), gastro-intestinal obstruction or impaction; hypersensitivity reported

Licensed use *IsoGel*® licensed for use in children (age range not specified by manufacturer)

Indications and dose

See under preparations

Counselling Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed

Fybogel® (Reckitt Benckiser)

Granules, buff, effervescent, sugar- and gluten-free, ispaghula husk 3.5 g/sachet (low Na⁺), net price 30 sachets (plain, lemon, or orange flavour) = £2.20. Label: 13, counselling, see above

Excipients include aspartame 16 mg/sachet (see section 9.4.1)

Dose

Constipation

- By mouth

Child 6–12 years ½–1 level 5-mL spoonful in water twice daily, preferably after meals

Child 12–18 years 1 sachet (or 2 level 5-mL spoonfuls) in water twice daily, preferably after meals

IsoGel® (Potters)

Granules, brown, sugar- and gluten-free, ispaghula husk 90%. Net price 200 g = £3.24. Label: 13, counselling, see above

Dose

Constipation

- By mouth

Child 6–12 years 1 level 5-mL spoonful in water once or twice daily, preferably at mealtimes

Child 12–18 years 2 level 5-mL spoonfuls in water once or twice daily, preferably at mealtimes

Note May be difficult to obtain

Ispagel Orange® (LPC)

Granules, beige, effervescent, sugar- and gluten-free, ispaghula husk 3.5 g/sachet, net price 30 sachets = £1.69. Label: 13, counselling, see above

Excipients include aspartame (section 9.4.1)

Dose

Constipation

- By mouth

Child 6–12 years ½–1 level 5-mL spoonful in water twice daily, preferably after meals

Child 12–18 years 1 sachet (or 2 level 5-mL spoonfuls) in water 1–3 times daily, preferably after meals

Regulan® (Procter & Gamble)

Powder, beige, sugar- and gluten-free, ispaghula husk 3.4 g/5.85-g sachet (orange or lemon/lime flavour). Net price 30 sachets = £2.44. Label: 13, counselling, see above

Excipients include aspartame (section 9.4.1)

Dose

Constipation

- By mouth

Child 6–12 years ½–1 level 5-mL spoonful in water 1–3 times daily, preferably after meals

Child 12–18 years 1 sachet in 150 mL water 1–3 times daily, preferably after meals

METHYLCELLULOSE

Cautions see under Ispaghula Husk

Contra-indications see under Ispaghula Husk; also infective bowel disease

Side-effects see under Ispaghula Husk

Licensed use no age limit specified by manufacturer

Indications and dose

See under preparations

Counselling Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed

Celevac® (AMCo)

Tablets, pink, scored, methylcellulose '450' 500 mg, net price 112-tab pack = £3.22. Counselling, see above and dose

Dose

Constipation, diarrhoea (see notes above)

- By mouth

Child 7–12 years 2 tablets twice daily

Child 12–18 years 3–6 tablets twice daily

Administration In constipation the dose should be taken with at least 300 mL liquid. In diarrhoea, ileostomy, and colostomy control, avoid liquid intake for 30 minutes before and after dose

STERCULIA**Cautions** see under *Ispaghula Husk***Contra-indications** see under *Ispaghula Husk***Pregnancy** manufacturer of *Normacol Plus*[®] advises avoid**Breast-feeding** manufacturer of *Normacol Plus*[®] advises avoid**Side-effects** see under *Ispaghula Husk***Indications and dose****Constipation** for dose see under preparation**Counselling** Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed**Normacol**[®] (Norgine)**Granules**, coated, gluten-free, sterculia 62%. Net price 500 g = £6.85; 60 × 7-g sachets = £5.77. Label: 25, 27, counselling, see above
Dose

• By mouth

Child 6–12 years ½–1 heaped 5-mL spoonful or the contents of ½–1 sachet, washed down without chewing with plenty of liquid once or twice daily after meals**Child 12–18 years** 1–2 heaped 5-mL spoonfuls or the contents of 1–2 sachets, washed down without chewing with plenty of liquid once or twice daily after meals**Administration** May be mixed with soft food (e.g. yoghurt) before swallowing, followed by plenty of liquid**Normacol Plus**[®] (Norgine)**Granules**, brown, coated, gluten-free, sterculia 62%, frangula (standardised) 8%. Net price 500 g = £7.32; 60 × 7 g sachets = £6.16. Label: 25, 27, Counselling, see above
Dose

• By mouth

Child 6–12 years ½–1 heaped 5-mL spoonful or the contents of ½–1 sachet, washed down without chewing with plenty of liquid, once or twice daily after meals**Child 12–18 years** 1–2 heaped 5-mL spoonfuls or the contents of 1–2 sachets, washed down without chewing with plenty of liquid, once or twice daily after meals

Glycerol suppositories act as a lubricant and as a rectal stimulant by virtue of the mildly irritant action of glycerol.

BISACODYL**Cautions** prolonged use (risk of electrolyte imbalance)**Contra-indications** intestinal obstruction, acute abdominal conditions, acute inflammatory bowel disease, severe dehydration**Pregnancy** see *Pregnancy*, p. 57**Side-effects** see notes above; nausea and vomiting; colitis also reported; *suppositories* local irritation**Indications and dose****Constipation** (tablets act in 10–12 hours; *suppositories* act in 20–60 minutes)

• By mouth

Child 4–18 years 5–20 mg once daily, adjusted according to response• By rectum (*suppositories*)**Child 2–18 years** 5–10 mg once daily, adjusted according to response**Bowel clearance before radiological procedures and surgery**

• By mouth and by rectum

Child 4–10 years *by mouth*, 5 mg at bedtime for 2 days before procedure and, if necessary, *by rectum*, 5 mg *suppository* 1 hour before procedure**Child 10–18 years** *by mouth*, 10 mg at bedtime for 2 days before procedure and, if necessary, *by rectum*, 10 mg *suppository* 1 hour before procedure**Bisacodyl** (Non-proprietary)**Tablets**, e/c, bisacodyl 5 mg, net price 100 = £3.43. Label: 5, 25**Suppositories**, bisacodyl 10 mg, net price 12 = £3.53**Paediatric suppositories**, bisacodyl 5 mg, net price 5 = 99p**Note** The brand name *Dulcolax*[®] (Boehringer Ingelheim) is used for bisacodyl tablets, net price 10-tab pack = 74p; *suppositories* (10 mg), 10 = £1.57; *paediatric suppositories* (5 mg), 5 = 94pThe brand name *Dulcolax*[®] *Pico Liquid* is used for sodium picosulfate elixir**1.6.2 Stimulant laxatives**Stimulant laxatives include **bisacodyl**, **sodium picosulfate**, and members of the **anthraquinone** group, **senna** and **danthron**. The indications for **danthron** are limited (see below) by its potential carcinogenicity (based on *rodent* carcinogenicity studies) and evidence of genotoxicity. Powerful stimulants such as **cascara** (an anthraquinone) and **castor oil** are obsolete. **Docusate sodium** probably acts both as a stimulant and as a softening agent.

Stimulant laxatives increase intestinal motility and often cause abdominal cramp; they should be avoided in intestinal obstruction. Stools should be softened by increasing dietary fibre and liquid or with an osmotic laxative (section 1.6.4) before giving a stimulant laxative. In chronic constipation, especially where withholding of stool occurs, additional doses of a stimulant laxative may be required. Long-term use of stimulant laxatives is sometimes necessary (see section 1.6), but excessive use can cause diarrhoea and related effects such as hypokalaemia.

DANTHRON
(Danthron)**Cautions** avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies)—risk of irritation and excoriation; *rodent* studies indicate potential carcinogenic risk**Contra-indications** see *Bisacodyl* above**Pregnancy** manufacturers of co-danthramer and co-danthrusate advise avoid—no information available**Breast-feeding** manufacturers of co-danthramer and co-danthrusate advise avoid—limited information available**Side-effects** see notes above; also urine may be coloured red**Indications and dose****Constipation in terminally ill children** for dose see under preparations

■ With poloxamer '188' (as co-danthramer)

Note Co-danthramer suspension 5 mL = one co-danthramer capsule, **but** strong co-danthramer suspension 5 mL = two strong co-danthramer capsules

Co-danthramer (Non-proprietary) (PoM)

Capsules, co-danthramer 25/200 (dantron 25 mg, poloxamer '188' 200 mg). Net price 60-cap pack = £12.86. Label: 14, (urine red)

Dose

● By mouth

Child 6–12 years 1 capsule at night (restricted indications, see notes above)

Child 12–18 years 1–2 capsules at night (restricted indications, see notes above)

Strong capsules, co-danthramer 37.5/500 (dantron 37.5 mg, poloxamer '188' 500 mg). Net price 60-cap pack = £15.55. Label: 14, (urine red)

Dose

● By mouth

Child 12–18 years 1–2 capsules at night (restricted indications, see notes above)

Suspension, co-danthramer 25/200 in 5 mL (dantron 25 mg, poloxamer '188' 200 mg/5 mL). Net price 300 mL = £103.60. Label: 14, (urine red)

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Brands include *Danlax*®

Dose

● By mouth

Child 2–12 years 2.5–5 mL at night (restricted indications, see notes above)

Child 12–18 years 5–10 mL at night (restricted indications, see notes above)

Strong suspension, co-danthramer 75/1000 in 5 mL (dantron 75 mg, poloxamer '188' 1 g/5 mL). Net price 300 mL = £252.50. Label: 14, (urine red)

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dose

● By mouth

Child 12–18 years 5 mL at night (restricted indications, see notes above)

■ With docusate sodium (as co-danthrusate)

Co-danthrusate (Non-proprietary) (PoM)

Capsules, co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg). Net price 63-cap pack = £42.50. Label: 14, (urine red)

Brands include *Normax*® JMS

Dose

● By mouth

Child 6–12 years 1 capsule at night (restricted indications, see notes above)

Child 12–18 years 1–3 capsules at night (restricted indications, see notes above)

Suspension, yellow, co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg/5 mL). Net price 200 mL = £8.75. Label: 14, (urine red)

Brands include *Normax*®

Dose

● By mouth

Child 6–12 years 5 mL at night (restricted indications, see notes above)

Child 12–18 years 5–15 mL at night (restricted indications, see notes above)

DOCUSATE SODIUM

(Diocetyl sodium sulphosuccinate)

Cautions see notes above; do not give with liquid paraffin

Contra-indications see notes above; also for *rectal preparations*, haemorrhoids or anal fissure

Pregnancy not known to be harmful—manufacturer advises caution

Breast-feeding present in milk following oral administration—manufacturer advises caution; rectal administration not known to be harmful

Side-effects see notes above; also rash

Licensed use *adult oral solution and capsules* not licensed for use in children under 12 years

Indications and dose

Constipation

● By mouth

Child 6 months–2 years 12.5 mg 3 times daily, adjusted according to response (use paediatric oral solution)

Child 2–12 years 12.5–25 mg 3 times daily, adjusted according to response (use paediatric oral solution)

Child 12–18 years up to 500 mg daily in divided doses, adjusted according to response

Note Oral preparations act within 1–2 days; response to rectal administration usually occurs within 20 minutes

Adjunct in abdominal radiological procedures

● By mouth

Child 12–18 years 400 mg with barium meal

Administration for administration *by mouth*, solution may be mixed with milk or squash

Diocetyl® (UCB Pharma)

Capsules, yellow/white, docusate sodium 100 mg, net price 30-cap pack = £2.09, 100-cap pack = £6.98

Docusol® (Typharm)

Adult oral solution, sugar-free, docusate sodium 50 mg/5 mL, net price 300 mL = £5.49

Paediatric oral solution, sugar-free, docusate sodium 12.5 mg/5 mL, net price 300 mL = £5.29

■ Rectal preparations

Norgalax Micro-enema® (Norgine)

Enema, docusate sodium 120 mg in 10-g single-dose disposable packs. Net price 10-g unit = 66p

Dose

● By rectum

Child 12–18 years 1 enema as a single dose

GLYCEROL

(Glycerin)

Indications and dose

Constipation

● By rectum

Child 1 month–1 year 1-g suppository as required

Child 1–12 years 2-g suppository as required

Child 12–18 years 4-g suppository as required

Glycerol Suppositories, BP

(Glycerin Suppositories)

Suppositories, gelatin 140 mg, glycerol 700 mg, purified water to 1 g, net price 12 = 88p (1 g), 88p (2 g), £1.77 (4 g)**Administration** Moisten with water before insertion**SENNA****Cautions** see notes above**Contra-indications** see notes above**Pregnancy** see Pregnancy, p. 57**Breast-feeding** not known to be harmful**Side-effects** see notes above**Licensed use** *tablets* not licensed for use in children under 6 years; *syrup* not licensed for use in children under 2 years**Indications and dose****Constitutional** for dose see under preparations**Note** Onset of action 8–12 hours; initial dose should be low**Senna** (Non-proprietary)**Tablets**, total sennosides (calculated as sennoside B) 7.5 mg. Net price 60 = £11.70**Brands include** *Senokot* **Dose**● **By mouth****Child 2–4 years** ½–2 tablets once daily, adjusted according to response**Child 4–6 years** ½–4 tablets once daily, adjusted according to response**Child 6–18 years** 1–4 tablets once daily, adjusted according to response**Manevac**® (HFA Healthcare)**Granules**, coated, senna fruit 12.4%, ispaghula 54.2%, net price 400 g = £9.25. Label: 25, counseling, administration**Excipients** include sucrose 800 mg per level 5-mL spoonful of granules**Dose**● **By mouth****Child 12–18 years** 1–2 level 5-mL spoonfuls at night with at least 150 mL water, fruit juice, milk, or warm drink**Counseling** Preparations that swell in contact with liquid should always be carefully swallowed with water or appropriate fluid and should not be taken immediately before going to bed**Senokot**® (Reckitt Benckiser)**Tablets** , see above**Syrup**, sugar-free, brown, total sennosides (calculated as sennoside B) 7.5 mg/5 mL. Net price 500 mL = £2.69**Dose**● **By mouth****Child 1 month–4 years** 2.5–10 mL once daily, adjusted according to response**Child 4–18 years** 2.5–20 mL once daily, adjusted according to response**SODIUM PICOSULFATE**

(Sodium picosulphate)

Cautions see notes above; active inflammatory bowel disease (avoid if fulminant)**Contra-indications** see notes above; severe dehydration**Pregnancy** see Pregnancy, p. 57**Breast-feeding** not known to be present in milk but manufacturer advises avoid unless potential benefit outweighs risk**Side-effects** see notes above; also nausea and vomiting**Licensed use** *elixir*, licensed for use in children (age range not specified by manufacturer); *Perles*® not licensed for use in children under 4 years**Indications and dose****Constipation**● **By mouth****Child 1 month–4 years** 2.5–10 mg once daily, adjusted according to response**Child 4–18 years** 2.5–20 mg once daily, adjusted according to response**Note** onset of action 6–12 hours**Bowel evacuation before abdominal radiological and endoscopic procedures on the colon, and surgery** section 1.6.5**Sodium Picosulfate** (Non-proprietary)**Elixir**, sodium picosulfate 5 mg/5 mL, net price 100 mL = £1.86**Note** The brand name *Dulcolax*® *Pico Liquid* (Boehringer Ingelheim) is used for sodium picosulfate elixir 5 mg/5 mL● **Bowel cleansing preparations**

Section 1.6.5

1.6.3 Faecal softenersEnemas containing **arachis oil** (ground-nut oil, peanut oil) lubricate and soften impacted faeces and promote a bowel movement.

Bulk laxatives (section 1.6.1) and non-ionic surfactant 'wetting' agents e.g. docusate sodium (section 1.6.2) also have softening properties. Such drugs are useful for oral administration in the management of anal fissure; glycerol suppositories (section 1.6.2) are useful for rectal use.

ARACHIS OIL**Cautions** intestinal obstruction; hypersensitivity to soya**Contra-indications** inflammatory bowel disease, hypersensitivity to arachis oil or peanuts**Licensed use** licensed for use in children (age range not specified by manufacturer)**Indications and dose****Impacted faeces**● **By rectum****Child 3–7 years** 45–65 mL as required**Child 7–12 years** 65–100 mL as required**Child 12–18 years** 100–130 mL as required**Administration** warm enema in warm water before use**Arachis Oil Enema** (Non-proprietary)**Enema**, arachis (peanut) oil in 130-mL single-dose disposable packs. Net price 130 mL = £7.98

1.6.4 Osmotic laxatives

Osmotic laxatives increase the amount of water in the large bowel, either by drawing fluid from the body into the bowel or by retaining the fluid they were administered with.

Lactulose is a semi-synthetic disaccharide which is not absorbed from the gastro-intestinal tract. It produces an osmotic diarrhoea of low faecal pH, and discourages the proliferation of ammonia-producing organisms. It is therefore useful in the treatment of *hepatic encephalopathy*.

Macrogols are inert polymers of ethylene glycol which sequester fluid in the bowel; giving fluid with macrogols may reduce the dehydrating effect sometimes seen with osmotic laxatives. Macrogols are an effective non-traumatic means of evacuation in children with faecal impaction and can be used in the long-term management of chronic constipation.

Saline purgatives such as **magnesium hydroxide** are commonly abused but are satisfactory for occasional use; adequate fluid intake should be maintained. **Magnesium salts** are useful where rapid bowel evacuation is required. **Sodium salts** should be avoided as they may give rise to sodium and water retention in susceptible individuals. **Phosphate enemas** are useful in bowel clearance before radiology, endoscopy, and surgery. Enemas containing **phosphate** or **sodium citrate**, and oral **bowel cleansing preparations** (section 1.6.5) should only be used on the advice of a specialist practitioner.

LACTULOSE

Cautions lactose intolerance; **interactions:** Appendix 1 (lactulose)

Contra-indications galactosaemia, intestinal obstruction

Pregnancy not known to be harmful; see also *Pregnancy*, p. 57

Side-effects nausea (can be reduced by administration with water, fruit juice or with meals), vomiting, flatulence, cramps, and abdominal discomfort

Licensed use not licensed for use in children for hepatic encephalopathy

Indications and dose

Constipation (may take up to 48 hours to act)

• By mouth

Child 1 month–1 year 2.5 mL twice daily, adjusted according to response

• **Child 1–5 years** 2.5–10 mL twice daily, adjusted according to response

• **Child 5–18 years** 5–20 mL twice daily, adjusted according to response

Hepatic encephalopathy

• By mouth

Child 12–18 years 30–50 mL 3 times daily; adjust dose to produce 2–3 soft stools per day

Lactulose (Non-proprietary)

Solution, lactulose 3.1–3.7 g/5 mL with other ketoses. Net price 300-mL = £1.85, 500-mL = £2.82; 10 × 15 mL sachet pack = £2.50

Brands include *Duphalac*®, *Lactugal*®, *Laevolac*®

MACROGOLS

(Polyethylene glycols)

Cautions discontinue if symptoms of fluid and electrolyte disturbance; see also preparations below

Contra-indications intestinal perforation or obstruction, paralytic ileus, severe inflammatory conditions of the intestinal tract (such as Crohn's disease, ulcerative colitis, and toxic megacolon); see also preparations below

Pregnancy limited data, but manufacturer advises that it can be used

Breast-feeding manufacturer advises that it can be used

Side-effects abdominal distension and pain, nausea, flatulence

Licensed use *Movicol*® *Paediatric Plain* not licensed for use in faecal impaction in children under 5 years, or for chronic constipation in children under 2 years

Indications and dose

See under preparations

Macrogol Oral Powder, Compound (Non-proprietary)

Oral powder, macrogol '3350' (polyethylene glycol '3350') 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/sachet, net price 20-sachet pack = £4.23, 30-sachet pack = £6.68. Label: 13, counselling, administration

Brands include *Laxido*® *Orange*, *Molaxole*®

Cautions patients with cardiovascular impairment should not take more than 2 sachets in any 1 hour

Dose

Chronic constipation

• By mouth

Child 12–18 years 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance, 1–2 sachets daily

Administration Mix contents of each sachet in half a glass (approx. 125 mL) of water

Faecal impaction

• By mouth

Child 12–18 years 4 sachets on first day, then increased in steps of 2 sachets daily to max. 8 sachets daily; total daily dose to be drunk within a 6 hour period. After disimpaction, switch to maintenance therapy

Administration Mix contents of 2 sachets in a glass (approx. 250 mL) of water. After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours

Movicol® (Norgine)

Oral powder, macrogol '3350' (polyethylene glycol '3350') 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/sachet, net price 20-sachet pack (lime- and lemon-flavoured) = £4.45, 30-sachet pack (lime- and lemon- or chocolate- or plain- flavoured) = £6.68, 50-sachet pack (lime- and lemon- or plain- flavoured) = £11.13. Label: 13, counselling, administration

Note Amount of potassium chloride varies according to flavour of *Movicol*® as follows: plain-flavour (sugar-free) = 50.2 mg/sachet; lime and lemon flavour = 46.6 mg/sachet; chocolate flavour = 31.7 mg/sachet. 1 sachet when reconstituted with 125 mL water provides K⁺ 5.4 mmol/litre

Cautions patients with cardiovascular impairment should not take more than 2 sachets in any 1 hour

Dose

Chronic constipation

• By mouth

Child 12–18 years 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance, 1–2 sachets daily

Administration Mix contents of each sachet in half a

glass (approx. 125 mL) of water

Faecal impaction

- By mouth

Child 12–18 years 4 sachets on first day, then increased in steps of 2 sachets daily to max. 8 sachets daily; total daily dose to be drunk within a 6 hour period. After disimpaction, switch to maintenance laxative therapy

Administration Mix contents of 2 sachets in a glass (approx. 250 mL) of water. After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours

Oral concentrate, macrogol '3350' (polyethylene glycol '3350') 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/25 mL, net price 500 mL (orange-flavoured) = £4.45. Label: 13, counselling, administration

Note 25 mL of oral concentrate when diluted with 100 mL water provides K^+ 5.4 mmol/litre

Dose

Chronic constipation

- By mouth

Child 12–18 years 25 mL 1–3 times daily, usually for up to 2 weeks; maintenance, 25 mL 1–2 times daily

Administration 25 mL of oral concentrate to be diluted with half a glass (approx. 100 mL) of water. After dilution the solution should be discarded if unused after 24 hours

Movicol®-Half (Norgine)

Oral powder, sugar-free, macrogol '3350' (polyethylene glycol '3350') 6.563 g, sodium bicarbonate 89.3 mg, sodium chloride 175.4 mg, potassium chloride 23.3 mg/sachet, net price 20-sachet pack (lime and lemon flavour) = £2.92, 30-sachet pack = £4.38. Label: 13, counselling, administration

Cautions patients with impaired cardiovascular function should not take more than 4 sachets in any 1 hour

Dose

Chronic constipation

- By mouth

Child 12–18 years 2–6 sachets daily in divided doses usually for up to 2 weeks; maintenance, 2–4 sachets daily

Administration Mix contents of each sachet in quarter of a glass (approx. 60–65 mL) of water

Faecal impaction

- By mouth

Child 12–18 years 8 sachets on first day, then increased in steps of 4 sachets daily to max. 16 sachets daily; total daily dose to be drunk within 6 hours. After disimpaction, switch to maintenance laxative therapy

Administration Mix contents of 4 sachets in a glass (approx. 250 mL) of water. After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours.

Movicol® Paediatric (Norgine) (PoM)

Oral powder, macrogol '3350' (polyethylene glycol '3350') 6.563 g, sodium bicarbonate 89.3 mg, sodium chloride 175.4 mg, potassium chloride 25.1 mg/sachet, net price 30-sachet pack (chocolate- or plain-flavoured) = £4.38. Label: 13, counselling, administration

Note Amount of potassium chloride varies according to flavour of Movicol® Paediatric as follows: chocolate flavour = 15.9 mg/sachet; plain flavour (sugar-free) = 25.1 mg/sachet. 1 sachet when reconstituted with 62.5 mL water provides K^+ 5.4 mmol/litre

Cautions with high doses, impaired gag reflex, reflux oesophagitis, impaired consciousness

Contra-indications cardiovascular impairment, renal impairment—no information available

Dose

Chronic constipation, prevention of faecal impaction

- By mouth

Child under 1 year ½–1 sachet daily

Child 1–6 years 1 sachet daily; adjust dose to produce regular soft stools (max. 4 sachets daily)

Child 6–12 years 2 sachets daily; adjust dose to produce regular soft stools (max. 4 sachets daily)

Administration Mix contents of each sachet in quarter of a glass (approx. 60–65 mL) of water

Faecal impaction

- By mouth

Child under 1 year ½–1 sachet daily

Child 1–5 years 2 sachets on first day, then 4 sachets daily for 2 days, then 6 sachets daily for 2 days, then 8 sachets daily. After disimpaction, switch to maintenance laxative therapy

Child 5–12 years 4 sachets on first day, then increased in steps of 2 sachets daily to max. 12 sachets daily. After disimpaction, switch to maintenance laxative therapy

Administration Mix contents of each sachet in quarter of a glass (approx. 60–65 mL) of water; total daily dose to be taken over a 12-hour period

MAGNESIUM SALTS

Cautions see also notes above; **interactions:** Appendix 1 (antacids)

Contra-indications acute gastro-intestinal conditions

Hepatic impairment avoid in hepatic coma if risk of renal failure

Renal impairment avoid or reduce dose; increased risk of toxicity

Side-effects colic

Indications and dose

Constipation see under preparations below

■ Magnesium hydroxide

Magnesium Hydroxide Mixture, BP

Aqueous suspension containing about 8% hydrated magnesium oxide. Do not store in cold place

Dose

- By mouth

Child 3–12 years 5–10 mL with water at bedtime when required

Child 12–18 years 30–45 mL with water at bedtime when required

■ Bowel cleansing preparations

Section 1.6.5

PHOSPHATES (RECTAL)

Cautions see notes above; also electrolyte disturbances, congestive heart failure, ascites, uncontrolled hypertension, maintain adequate hydration

Contra-indications acute gastro-intestinal conditions (including gastro-intestinal obstruction, inflammatory bowel disease, and conditions associated with increased colonic absorption)

Renal impairment use with caution

Side-effects local irritation, electrolyte disturbances

Indications and dose

Constipation, bowel evacuation before abdominal radiological procedures, endoscopy, and surgery

For dose see preparations

Fleet® Ready-to-use Enema (Casen-Fleet)

Enema, sodium acid phosphate 21.4 g, sodium phosphate 9.4 g/118 mL, net price 133-mL pack (delivers 118 mL dose) with standard tube = 68p

Dose

● By rectum

Child 3–7 years 40–60 mL once daily

Child 7–12 years 60–90 mL once daily

Child 12–18 years 90–118 mL once daily

Phosphates Enema BP Formula B

Enema, sodium dihydrogen phosphate dihydrate 12.8 g, disodium phosphate dodecahydrate 10.24 g, purified water, freshly boiled and cooled, to 128 mL. Net price 128 mL with standard tube = £2.98, with long rectal tube = £9.70

Dose

● By rectum

Child 3–7 years 45–65 mL once daily

Child 7–12 years 65–100 mL once daily

Child 12–18 years 100–128 mL once daily

SODIUM CITRATE (RECTAL)

Cautions see notes above

Contra-indications acute gastro-intestinal conditions

Indications and dose

Constipation for dose see under preparations

Micolette Micro-enema® (Pinewood)

Enema, sodium citrate 450 mg, sodium lauryl sulfoacetate 45 mg, glycerol 625 mg, together with citric acid, potassium sorbate, and sorbitol in a viscous solution, in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 41p

Dose

● By rectum

Child 3–18 years 5–10 mL as a single dose

Miralax Micro-enema® (RPH)

Enema, sodium citrate 450 mg, sodium alkylsulfoacetate 45 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 41p

Dose

● By rectum

Child 3–18 years 5 mL as a single dose

Relaxit Micro-enema® (Crawford)

Enema, sodium citrate 450 mg, sodium lauryl sulfate 75 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 43p

Dose

● By rectum

Child 1 month–18 years 5 mL as a single dose (insert only half nozzle length in child under 3 years)

1.6.5 Bowel cleansing preparations

Bowel cleansing preparations are used before colonic surgery, colonoscopy, or radiological examination to ensure the bowel is free of solid contents. They are not treatments for constipation.

Cautions Bowel cleansing preparations should be used with caution in children, particularly in those

with fluid and electrolyte disturbances. Renal function should be measured before starting treatment in patients at risk of fluid and electrolyte disturbances. Hypovolaemia should be corrected before administration of bowel cleansing preparations. Adequate hydration should be maintained during treatment. Bowel cleansing preparations should be used with caution in colitis (avoid if acute severe colitis), or in those who are debilitated. Other oral drugs should not be taken one hour before or after administration of bowel cleansing preparations because absorption may be impaired.

Contra-indications Bowel cleansing preparations are contra-indicated in patients with gastro-intestinal obstruction or perforation, gastric retention, acute severe colitis, or toxic megacolon.

Side-effects Side-effects of bowel cleansing preparations include nausea, vomiting, abdominal pain (usually transient—reduced by taking more slowly), and abdominal distention. Less frequent side-effects include headache, dizziness, dehydration, and electrolyte disturbances.

MACROGOLS

Cautions see notes above; also heart failure

Contra-indications see notes above; also gastro-intestinal ulceration

Pregnancy manufacturers advise use only if essential—no information available

Breast-feeding manufacturers advise use only if essential—no information available

Side-effects see notes above; also anal discomfort

Licensed use *Klean-Prep®* not licensed for use in children

Indications and dose

See preparations

Klean-Prep® (Norgine)

Oral powder, sugar-free, macrogol '3350' (polyethylene glycol '3350') 59 g, anhydrous sodium sulfate 5.685 g, sodium bicarbonate 1.685 g, sodium chloride 1.465 g, potassium chloride 743 mg/sachet, net price 4 sachets = £9.07. Label: 10, patient information leaflet, counselling

Excipients include aspartame (section 9.4.1)

Electrolytes 1 sachet when reconstituted with 1 litre water provides Na^+ 125 mmol, K^+ 10 mmol, Cl^- 35 mmol, HCO_3^- 20 mmol

Dose

Bowel cleansing before radiological examination, colonoscopy, or surgery

● By mouth

Child 12–18 years 2 litres of reconstituted solution on the evening before procedure and 2 litres of reconstituted solution on the morning of procedure; alternatively, a glass (approx. 250 mL) of reconstituted solution every 10–15 minutes, or by nasogastric tube 20–30 mL/minute, starting on the day before procedure until 4 litres have been consumed. Treatment can be stopped if bowel motions become watery and clear.

Distal intestinal obstruction syndrome

● By mouth, nasogastric or gastrostomy tube

Child 1–18 years 10 mL/kg/hour for 30 minutes, then 20 mL/kg/hour for 30 minutes, then increase to 25 mL/kg/hour if tolerated; max. 100 mL/kg (or 4 litres) over 4 hours; repeat 4-hour treatment if necessary

Administration 1 sachet should be reconstituted with 1 litre of water. Flavouring such as clear fruit cordials may be added if required. Solid food should not be taken for at least 2 hours before starting treatment. After reconstitution the solution should be kept in a refrigerator and discarded if unused after 24 hours.

MAGNESIUM CITRATE

Reconstitution of a sachet containing 11.57 g magnesium carbonate and 17.79 g anhydrous citric acid produces a solution containing magnesium citrate

Cautions see notes above

Contra-indications see notes above

Hepatic impairment avoid in hepatic coma if risk of renal failure

Renal impairment avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—risk of hypermagnesaemia

Pregnancy caution

Breast-feeding caution

Side-effects see notes above

Indications and dose

See preparations

Citramag® (Sanochemia)

Oral powder, sugar-free, effervescent, magnesium carbonate 11.57 g, anhydrous citric acid 17.79 g/sachet, net price 10-sachet pack (lemon and lime flavour) = £18.92. Label: 10, patient information leaflet, 13, counselling, see below

Electrolytes Mg²⁺ 118 mmol/sachet

Dose

Bowel evacuation on day before radiological examination, colonoscopy, or surgery

• By mouth

Child 5–10 years on day before procedure, one-third of a sachet at 8 a.m. and one-third of a sachet between 2 and 4 p.m.

Child 10–18 years on day before procedure, ½–1 sachet at 8 a.m. and ½–1 sachet between 2 and 4 p.m.

Counselling One sachet should be reconstituted with 200 mL of hot water; the solution should be allowed to cool for approx. 30 minutes before drinking. Low residue or fluid only diet (e.g. water, fruit squash, lemonade, clear soup, black tea or coffee) recommended before procedure (according to hospital advice) and copious intake of clear fluids recommended until procedure

SODIUM PICOSULFATE WITH MAGNESIUM CITRATE

Cautions see notes above; also recent gastro-intestinal surgery; cardiac disease (avoid in congestive cardiac failure)

Contra-indications see notes above; also gastro-intestinal ulceration; ascites; congestive cardiac failure

Hepatic impairment avoid in hepatic coma if risk of renal failure

Renal impairment avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—risk of hypermagnesaemia

Pregnancy caution

Breast-feeding caution

Side-effects see notes above; also anal discomfort, sleep disturbances, fatigue, and rash

Indications and dose

See preparations

Picolax® (Ferring)

Oral powder, sugar-free, sodium picosulfate 10 mg/sachet, with magnesium citrate, net price 20-sachet pack = £33.90. Label: 10, patient information leaflet, 13, counselling, see below

Electrolytes K⁺ 5 mmol, Mg²⁺ 87 mmol/sachet

Dose

Bowel evacuation on day before radiological procedure, endoscopy, or surgery

• By mouth

Child 1–2 years ¼ sachet before 8 a.m. then ¼ sachet 6–8 hours later

Child 2–4 years ½ sachet before 8 a.m. then ½ sachet 6–8 hours later

Child 4–9 years 1 sachet before 8 a.m. then ½ sachet 6–8 hours later

Child 9–18 years 1 sachet before 8 a.m. then 1 sachet 6–8 hours later

Note Acts within 3 hours of first dose. Low residue diet recommended on the day before procedure and copious intake of water or other clear fluids recommended during treatment

Counselling One sachet should be reconstituted with 150 mL (approx. half a glass) of cold water; children and carers should be warned that heat is generated during reconstitution and that the solution should be allowed to cool before drinking

Amidotrizoates

Gastrografin® is an **amidotrizoate** radiological contrast medium with high osmolality; it is used in the treatment of meconium ileus in neonates and in the management of distal intestinal obstruction syndrome in children with cystic fibrosis.

AMIDOTRIZOATES

Diatrizoates

Cautions asthma or history of allergy, latent hyperthyroidism, dehydration and electrolyte disturbance (correct first); in children with oesophageal fistulae (aspiration may lead to pulmonary oedema); benign nodular goitre; enteritis; risk of anaphylactoid reactions increased by concomitant administration of beta-blockers

Contra-indications hypersensitivity to iodine, hyperthyroidism

Pregnancy manufacturer advises caution

Breast-feeding amount probably too small to be harmful

Side-effects diarrhoea, nausea, vomiting; also reported, abdominal pain, intestinal perforation, bowel necrosis, oral mucosal blistering, hypersensitivity reactions, pyrexia, headache, dizziness, disturbances in consciousness, hyperthyroidism, electrolyte disturbances, and skin reactions (including toxic epidermal necrolysis)

Licensed use not licensed for use in distal intestinal obstruction syndrome

Indications and dose

Uncomplicated meconium ileus

• By rectum

Neonate 15–30 mL as a single dose

Distal intestinal obstruction syndrome

• By mouth or by rectum

Child 1 month–2 years 15–30 mL as a single dose

Child body-weight 15–25 kg 50 mL as a single dose

Child body-weight over 25 kg 100 mL as a single dose

Administration Intravenous prehydration is essential in neonates and infants. Fluid intake should be encouraged for 3 hours after administration. *By mouth*,

for child bodyweight under 25 kg, dilute *Gastrografin*® with 3 times its volume of water or fruit juice; for child bodyweight over 25 kg, dilute *Gastrografin*® with twice its volume of water or fruit juice. *By rectum*, administration must be carried out slowly under radiological supervision to ensure required site is reached. For child under 5 years, dilute *Gastrografin*® with 5 times its volume of water; for child over 5 years dilute *Gastrografin*® with 4 times its volume of water.

Radiological investigations dose to be recommended by radiologist

Gastrografin® (Bayer Schering)

Solution, sodium amidotrizoate 100 mg, meglumine amidotrizoate 660 mg/mL, net price 100-mL bottle = £14.69

Excipients include disodium edetate

1.6.6 Peripheral opioid-receptor antagonists

Classification not used in *BNF for Children*.

1.6.7 Other drugs used in constipation

Classification not used in *BNF for Children*.

1.7 Local preparations for anal and rectal disorders

1.7.1 Soothing anal and rectal preparations

1.7.2 Compound anal and rectal preparations with corticosteroids

1.7.3 Rectal sclerosants

1.7.4 Management of anal fissures

In children with perianal soreness or pruritus ani, good toilet hygiene is essential; the use of alcohol-free 'wet-wipes' after each bowel motion, regular bathing and the avoidance of local irritants such as bath additives is recommended. Excoriated skin is best treated with a protective barrier emollient (section 13.2.2); in children over 1 month, **hydrocortisone** ointment or cream (section 13.4) or a compound rectal preparation (section 1.7.2) may be used for a short period of time, up to a maximum of 7 days.

Pruritus ani caused by threadworm infection requires treatment with an anthelmintic (section 5.5.1). Topical application of **white soft paraffin** or other bland emollient (section 13.2.1) may reduce anal irritation caused by threadworms.

Perianal erythema caused by streptococcal infection should be treated initially with an oral antibacterial such as **phenoxymethylpenicillin** (section 5.1.1.1) or **erythromycin** (section 5.1.5), while awaiting results of culture and sensitivity testing.

Perianal candidiasis (thrush) requires treatment with a topical antifungal preparation (section 13.10.2). For treatment of vulvovaginal candidiasis, see section 7.2.2.

Proctitis associated with inflammatory bowel disease in children is treated with corticosteroids and aminosalicylates (section 1.5).

For the management of anal fissures, see section 1.7.4.

1.7.1 Soothing anal and rectal preparations

Haemorrhoids in children are rare, but may occur in infants with portal hypertension. Soothing rectal preparations containing mild astringents such as bismuth subgallate, zinc oxide, and hamamelis may provide symptomatic relief, but proprietary preparations which also contain lubricants, vasoconstrictors, or mild anti-septics may cause further perianal irritation.

Local anaesthetics may be used to relieve pain in children with anal fissures or pruritus ani, but local anaesthetics are absorbed through the rectal mucosa and may cause sensitisation of the anal skin. Excessive use of local anaesthetics may result in systemic effects, see section 15.2. Preparations containing local anaesthetics should be used for no longer than 2–3 days.

Lidocaine ointment (section 15.2) may be applied before defaecation to relieve pain associated with anal fissure, but local anaesthetics can cause stinging initially and this may aggravate the child's fear of pain.

Other local anaesthetics such as tetracaine, cinchocaine (dibucaine), and pramocaine (pramoxine) may be included in rectal preparations, but these are more irritant than lidocaine.

Corticosteroids are often combined with local anaesthetics and soothing agents in topical preparations for haemorrhoids and proctitis. Topical preparations containing corticosteroids (section 1.7.2) should not be used long-term or if infection (such as herpes simplex) is present. For further information on the use of topical corticosteroids, see section 13.4.

1.7.2 Compound anal and rectal preparations with corticosteroids

Anusgesic-HC® (Pfizer) (PoM)

Cream, benzyl benzoate 1.2%, bismuth oxide 0.875%, hydrocortisone acetate 0.5%, Peru balsam 1.85%, pramocaine hydrochloride 1%, zinc oxide 12.35%. Net price 30 g (with rectal nozzle) = £3.71

Dose

Haemorrhoids, pruritus ani

• **By rectum**

Child 12–18 years apply night and morning and after a bowel movement; do not use for longer than 7 days

Suppositories, buff, benzyl benzoate 33 mg, bismuth oxide 24 mg, bismuth subgallate 59 mg, hydrocortisone acetate 5 mg, Peru balsam 49 mg, pramocaine hydrochloride 27 mg, zinc oxide 296 mg, net price 12 = £2.69

Dose

Haemorrhoids, pruritus ani

• **By rectum**

Child 12–18 years insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days

Anusol-HC® (McNeil) (PoM)

Ointment, benzyl benzoate 1.25%, bismuth oxide 0.875%, bismuth subgallate 2.25%, hydrocortisone acetate 0.25%, Peru balsam 1.875%, zinc oxide 10.75%. Net price 30 g (with rectal nozzle) = £2.49

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 12–18 years apply night and morning and after a bowel movement; do not use for longer than 7 days

Suppositories, benzyl benzoate 33 mg, bismuth oxide 24 mg, bismuth subgallate 59 mg, hydrocortisone acetate 10 mg, Peru balsam 49 mg, zinc oxide 296 mg. Net price 12 = £1.74

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 12–18 years insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days

Perinal® (Dermal)

Spray application, hydrocortisone 0.2%, lidocaine hydrochloride 1%. Net price 30-mL pack = £6.11

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 2–18 years spray once over the affected area up to 3 times daily; do not use for longer than 7 days without medical advice (child under 14 years, on medical advice only)

Proctofoam HC® (Meda) (PoM)

Foam in aerosol pack, hydrocortisone acetate 1%, pramocaine hydrochloride 1%. Net price 21.2-g pack (approx. 40 applications) with applicator = £6.07

Dose**Pain and irritation associated with local, non-infected anal or perianal conditions**

- By rectum

Child 12–18 years 1 applicatorful (4–6 mg hydrocortisone acetate, 4–6 mg pramocaine hydrochloride) by rectum 2–3 times daily and after a bowel movement (max. 4 times daily); do not use for longer than 7 days

Proctosedyl® (Sanofi-Aventis) (PoM)

Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, hydrocortisone 0.5%, net price 30 g = £10.34 (with cannula)

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 1 month–18 years apply morning and night and after a bowel movement, externally or by rectum; do not use for longer than 7 days

Suppositories, cinchocaine (dibucaine) hydrochloride 5 mg, hydrocortisone 5 mg, net price 12 = £5.08

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 12–18 years insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days

Scheriproct® (Bayer) (PoM)

Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, prednisolone hexanoate 0.19%, net price 30 g = £2.94

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 1 month–18 years apply twice daily for 5–7 days (3–4 times daily on 1st day if necessary), then once daily for a few days after symptoms have cleared

Suppositories, cinchocaine (dibucaine) hydrochloride 1 mg, prednisolone hexanoate 1.3 mg, net price 12 = £1.38

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 12–18 years insert 1 suppository daily after a bowel movement, for 5–7 days (in severe cases initially 2–3 times daily)

Ultraproct® (Meadow) (PoM)

Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, fluocortolone caproate 0.095%, fluocortolone pivalate 0.092%, net price 30 g (with rectal nozzle) = £4.57

Dose**Haemorrhoids, pruritus ani**

Child 1 month–18 years apply twice daily for 5–7 days (3–4 times daily on 1st day if necessary), then once daily for a few days after symptoms have cleared

Suppositories, cinchocaine (dibucaine) hydrochloride 1 mg, fluocortolone caproate 630 micrograms, fluocortolone pivalate 610 micrograms, net price 12 = £2.15

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 12–18 years insert 1 suppository daily after a bowel movement, for 5–7 days (in severe cases initially 2–3 times daily) then 1 suppository every other day for 1 week

Uniroid-HC® (Chemidex) (PoM)

Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, hydrocortisone 0.5%, net price 30 g (with applicator) = £4.23

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 1 month–18 years apply twice daily and after a bowel movement, externally or by rectum; do not use for longer than 7 days (child under 12 years, on medical advice only)

Suppositories, cinchocaine (dibucaine) hydrochloride 5 mg, hydrocortisone 5 mg, net price 12 = £1.91

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 12–18 years insert 1 suppository twice daily and after a bowel movement; do not use for longer than 7 days

Xyloproct® (AstraZeneca) (PoM)

Ointment (water-miscible), aluminium acetate 3.5%, hydrocortisone acetate 0.275%, lidocaine 5%, zinc oxide 18%, net price 20 g (with applicator) = £4.19

Dose**Haemorrhoids, pruritus ani**

- By rectum

Child 1 month–18 years apply several times daily; short-term use only

1.7.3 Rectal sclerosants

Classification not used in *BNF for Children*.

1.7.4 Management of anal fissures

The management of anal fissures includes stool softening (section 1.6) and the short-term use of a topical preparation containing a local anaesthetic (section 1.7.1). If these measures are inadequate, children with chronic anal fissures should be referred for specialist treatment in hospital. Topical **glyceryl trinitrate**, 0.05% or 0.1% ointment, may be used in children to relax the anal sphincter, relieve pain and aid healing of anal fissures. Excessive application of topical nitrates causes side-effects such as headache, flushing, dizziness, and postural hypotension.

Before considering surgery, **diltiazem** 2% ointment may be used in children with chronic anal fissures resistant to topical nitrates.

Ointments containing glyceryl trinitrate in a range of strengths or diltiazem 2% are available as manufactured specials (see Special-order Manufacturers, p. 840).

1.8 Stoma and enteral feeding tubes

Stoma

Prescribing for children with stoma calls for special care. The following is a brief account of some of the main points to be borne in mind.

When a solid-dose formulation such as a capsule or a tablet is given the contents of the ostomy bag should be checked for any remnants; response to treatment should be carefully monitored because of the possibility of incomplete absorption. *Enteric-coated* and *modified-release* preparations are **unsuitable**, particularly in children with an ileostomy, as there may not be sufficient release of the active ingredient.

Laxatives Enemas and washouts should be used in children with stoma only under specialist supervision; they should **not** be prescribed for those with an ileostomy as they may cause rapid and severe loss of water and electrolytes.

Children with colostomy may suffer from constipation and whenever possible it should be treated by increasing fluid intake or dietary fibre. If a laxative (section 1.6) is required, it should generally be used for short periods only.

Antidiarrhoeals **Loperamide**, **codeine phosphate**, and **co-phenotrope** (section 1.4.2) are effective for controlling excessive stool losses. Bulk-forming drugs (section 1.6.1) may be tried but it is often difficult to adjust the dose appropriately.

Antibacterials should **not** be given for an episode of acute diarrhoea.

Antacids The tendency to diarrhoea from magnesium salts or constipation from aluminium salts may be increased in children with stoma.

Diuretics Diuretics should be used with caution in children with an ileostomy because they may become excessively dehydrated and potassium depletion may easily occur. It is usually advisable to use a **potassium-sparing** diuretic (section 2.2.3).

Digoxin Children with stoma are particularly susceptible to hypokalaemia. This predisposes children on digoxin to digoxin toxicity; potassium supplements (section 9.2.1.1) or a potassium-sparing diuretic (section 2.2.3) may be advisable.

Analgesics Opioid analgesics (section 4.7.2) may cause troublesome constipation in children with colostomy. When a non-opioid analgesic is required **paracetamol** is usually suitable; anti-inflammatory analgesics may cause gastric irritation and bleeding.

Iron preparations Iron supplements may cause loose stools and sore skin at the stoma site. If this is troublesome and if iron is definitely indicated a parenteral iron preparation (section 9.1.1.2) should be used. Modified-release iron preparations should be **avoided**.

Care of stoma Children and carers are usually given advice about the use of *cleansing agents*, *protective creams*, *lotions*, *deodorants*, or *sealants* whilst in hospital, either by the surgeon or by a stoma-care nurse. Voluntary organisations offer help and support to patients with stoma.

Enteral feeding tubes

Care is required in choosing an appropriate formulation of a drug for administration through a nasogastric narrow-bore feeding tube or through a percutaneous endoscopic gastrostomy (PEG) or jejunostomy tube. Liquid preparations (or soluble tablets) are preferred; injection solutions may also be suitable for administration through an enteral tube.

If a solid formulation of a medicine needs to be given, it should be given as a suspension of particles fine enough to pass through the tube. It is possible to crush many immediate-release tablets but enteric-coated or modified-release preparations should **not** be crushed.

Enteral feeds may affect the absorption of drugs and it is therefore important to consider the timing of drug administration in relation to feeds. If more than one drug needs to be given, they should be given separately and the tube should be flushed with water after each drug has been given.

Clearing blockages Carbonated (sugar-free) drinks may be marginally more effective than water in unblocking feeding tubes, but mildly acidic liquids (such as pineapple juice or cola-based drinks) can coagulate protein in feeds, causing further blockage. If these measures fail to clear the enteral feeding tube, an alkaline solution containing pancreatic enzymes may be introduced into the tube (followed after at least 5 minutes by water). Specific products designed to break up blockages caused by formula feeds are also available.

1.9 Drugs affecting intestinal secretions

- 1.9.1 Drugs affecting biliary composition and flow
- 1.9.2 Bile acid sequestrants
- 1.9.3 Aprotinin
- 1.9.4 Pancreatin

1.9.1 Drugs affecting biliary composition and flow

Bile acids (**ursodeoxycholic** and **chenodeoxycholic acid**) may be used as dietary supplements in children with inborn errors of bile acid synthesis. Ursodeoxycholic acid is used to improve the flow of bile in children with cholestatic conditions such as familial intrahepatic cholestasis, biliary atresia in infants, cystic-fibrosis-related liver disease, and cholestasis caused by total parenteral nutrition or following liver transplantation. Ursodeoxycholic acid may also relieve the severe itching associated with cholestasis.

In sclerosing cholangitis, ursodeoxycholic acid is used to lower liver enzyme and serum-bilirubin concentrations.

Ursodeoxycholic acid is also used in the treatment of intrahepatic cholestasis in pregnancy.

Smith-Lemli-Opitz syndrome Chenodeoxycholic and ursodeoxycholic acid have been used with cholesterol in children with Smith-Lemli-Opitz syndrome. Chenodeoxycholic acid is also used in combination with cholic acid to treat bile acid synthesis defects but cholic acid is difficult to obtain. Chenodeoxycholic acid and cholesterol are available from 'special-order' manufacturers or specialist importing companies, see p. 840.

URSODEOXYCHOLIC ACID

Cautions interactions: Appendix 1 (bile acids)

Contra-indications radio-opaque stones; non-functioning gall bladder (in patients with radiolucent gallstones)

Hepatic impairment avoid in chronic liver disease (but used in primary biliary cirrhosis)

Pregnancy no evidence of harm but manufacturer advises avoid

Breast-feeding not known to be harmful but manufacturer advises avoid

Side-effects rarely, diarrhoea

Licensed use not licensed for use in children for indications shown below

Indications and dose

Cholestasis

- By mouth

Neonate 5 mg/kg 3 times daily, adjust dose and frequency according to response, max. 10 mg/kg 3 times daily

Child 1 month–2 years 5 mg/kg 3 times daily, adjust dose and frequency according to response, max. 10 mg/kg 3 times daily

Improvement of hepatic metabolism of essential fatty acids and bile flow, in children with cystic fibrosis

- By mouth

Child 1 month–18 years 10–15 mg/kg twice daily; total daily dose may alternatively be given in 3 divided doses

Cholestasis associated with total parenteral nutrition

- By mouth

Neonate 10 mg/kg 3 times daily

Child 1 month–18 years 10 mg/kg 3 times daily

Sclerosing cholangitis

- By mouth

Child 1 month–18 years 5–10 mg/kg 2–3 times daily, adjusted according to response, max. 15 mg/kg 3 times daily

Ursodeoxycholic Acid (Non-proprietary) (PoM)

Tablets, ursodeoxycholic acid 150 mg, net price 60-tab pack = £13.45; 300 mg, 60-tab pack = £38.86. Label: 21

Capsules, ursodeoxycholic acid 250 mg, net price 60-cap pack = £25.29. Label: 21

Destolit® (Norgine) (PoM)

Tablets, scored, ursodeoxycholic acid 150 mg, net price 60-tab pack = £18.39. Label: 21

Ursofalk® (Dr Falk) (PoM)

Capsules, ursodeoxycholic acid 250 mg, net price 60-cap pack = £30.17, 100-cap pack = £31.88. Label: 21

Tablets, f/c, scored, ursodeoxycholic acid 500 mg, net price 100-tab pack = £80.00. Label: 21

Suspension, sugar-free, ursodeoxycholic acid 250 mg/5 mL, net price 250 mL = £26.98. Label: 21

Ursogal® (Galen) (PoM)

Tablets, scored, ursodeoxycholic acid 150 mg, net price 60-tab pack = £14.49. Label: 21

Capsules, ursodeoxycholic acid 250 mg, net price 60-cap pack = £25.93. Label: 21

Other preparations for bile synthesis defects

CHENODEOXYCHOLIC ACID

Cautions see under Ursodeoxycholic Acid; interactions: Appendix 1 (bile acids)

Contra-indications see under Ursodeoxycholic Acid

Pregnancy avoid—fetotoxicity reported in *animal* studies

Side-effects see under Ursodeoxycholic Acid

Licensed use not licensed

Indications and dose

Cerebrotendinous xanthomatosis

- By mouth

Neonate 5 mg/kg 3 times daily

Child 1 month–18 years 5 mg/kg 3 times daily

Defective synthesis of bile acid

● By mouth

Neonate initially 5 mg/kg 3 times daily, reduced to 2.5 mg/kg 3 times daily

Child 1 month–18 years initially 5 mg/kg 3 times daily, reduced to 2.5 mg/kg 3 times daily

Smith-Lemli-Opitz syndrome see notes above

● By mouth

Neonate 7 mg/kg once daily or in divided doses

Child 1 month–18 years 7 mg/kg once daily or in divided doses

Administration for administration *by mouth*, add the contents of a 250-mg capsule to 25 mL of sodium bicarbonate solution 8.4% (1 mmol/mL) to produce a suspension containing chenodeoxycholic acid 10 mg/mL; use immediately after preparation, discard any remaining suspension

Chenodeoxycholic acid (Non-proprietary) (PoM)

Capsules, chenodeoxycholic acid 250 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

CHOLESTEROL

Cautions consult product literature

Contra-indications consult product literature

Licensed use not licensed

Indications and dose**Smith-Lemli-Opitz syndrome**

● By mouth

Neonate 5–10 mg/kg 3–4 times daily

Child 1 month–18 years 5–10 mg/kg 3–4 times daily (doses up to 15 mg/kg 4 times daily have been used)

Administration cholesterol powder can be mixed with a vegetable oil before administration

Cholesterol Powder (Non-proprietary)

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

1.9.2 Bile acid sequestrants

Colestyramine is an anion-exchange resin that forms an insoluble complex with bile acids in the gastro-intestinal tract; it is used to relieve diarrhoea associated with surgical procedures such as ileal resection, or following radiation therapy. Colestyramine is also used in the treatment of familial hypercholesterolaemia (see section 2.12), and to relieve pruritus in children with partial biliary obstruction, (for treatment of pruritus, see section 3.4.1). Colestyramine is not absorbed from the gastro-intestinal tract, but will interfere with the absorption of a number of drugs, so timing of administration is important.

COLESTYRAMINE
(Cholestyramine)

Cautions section 2.12

Contra-indications section 2.12

Pregnancy section 2.12

Breast-feeding section 2.12

Side-effects section 2.12

Licensed use not licensed for use in children under 6 years

Indications and dose

Pruritus associated with partial biliary obstruction and primary biliary cirrhosis, diarrhoea associated with Crohn's disease, ileal resection, vagotomy, diabetic vagal neuropathy, and radiation

● By mouth

Child 1 month–1 year 1 g once daily in a suitable liquid, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 9 g daily)

Child 1–6 years 2 g once daily in a suitable liquid, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 18 g daily)

Child 6–12 years 4 g once daily in a suitable liquid, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 24 g daily)

Child 12–18 years 4–8 g once daily in a suitable liquid, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 36 g daily)

Counselling Other drugs should be taken at least 1 hour before or 4–6 hours after colestyramine to reduce possible interference with absorption

Note For treatment of diarrhoea induced by bile acid malabsorption, if no response within 3 days an alternative therapy should be initiated

Hypercholesterolaemia section 2.12

Administration The contents of one sachet should be mixed with at least 150 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, or pulpy fruits with a high moisture content

Preparations

Section 2.12

1.9.3 Aprotinin

Classification not used in *BNF for Children*.

1.9.4 Pancreatin

Pancreatin, containing a mixture of protease, lipase and amylase in varying proportions, aids the digestion of starch, fat, and protein. Supplements of pancreatin are given by mouth to compensate for reduced or absent exocrine secretion in cystic fibrosis, and following pancreatotomy, total gastrectomy, or chronic pancreatitis.

The dose of pancreatin is adjusted according to size, number, and consistency of stools, and the nutritional status of the child; extra allowance will be needed if snacks are taken between meals. Daily dose should not exceed 10 000 lipase units per kg body-weight per day, (**important**: see advice on Higher-strength preparations below).

Pancreatin preparations

Preparation	Protease units	Amylase units	Lipase units
Creon® 10 000 capsule, e/c granules	600	8000	10 000
Creon® Micro e/c granules (per 100 mg)	200	3600	5000
Pancrex® granules (per gram)	300	4000	5000
Pancrex V® capsule, powder	430	9000	8000
Pancrex V '125'® capsule, powder	160	3300	2950
Pancrex V® e/c tablet	110	1700	1900
Pancrex V® Forte e/c tablet	330	5000	5600
Pancrex V® powder (per gram)	1400	30 000	25 000

Higher-strength pancreatin preparations *Pancrease HL*® and *Nutrizym 22*® have been associated with the development of large bowel strictures (fibrosing colonopathy) in children with cystic fibrosis aged between 2 and 13 years. The following is recommended:

- *Pancrease HL*®, *Nutrizym 22*® should not be used in children under 16 years with cystic fibrosis;
- the total dose of pancreatic enzyme supplements used in patients with cystic fibrosis should not usually exceed 10 000 units of lipase per kg body-weight daily;
- if a patient on any pancreatin preparation develops new abdominal symptoms (or any change in existing abdominal symptoms) the patient should be reviewed to exclude the possibility of colonic damage.

Possible risk factors are gender (boys at greater risk than girls), more severe cystic fibrosis, and concomitant use of laxatives. The peak age for developing fibrosing colonopathy is between 2 and 8 years.

Higher-strength pancreatin preparations

Preparation	Protease units	Amylase units	Lipase units
Creon® 25 000 capsule, e/c pellets	1000	18 000	25 000
Creon® 40 000 capsule, e/c granules	1600	25 000	40 000
Nutrizym 22® capsule, e/c minitabets	1100	19 800	22 000
Pancrease HL® capsule, e/c minitabets	1250	22 500	25 000

Pancreatin is inactivated by gastric acid therefore pancreatin preparations are best taken with food (or immediately before or after food). In children with cystic fibrosis with persistent fat malabsorption despite optimal use of enzyme replacement, an **H₂-receptor antagonist** (section 1.3.1), or a **proton pump inhibitor** (section 1.3.5) may improve fat digestion and absorption. Enteric-coated preparations are designed to deliver a higher enzyme concentration in the duodenum (provided the capsule contents are swallowed whole without chewing). If the capsules are opened the enteric-coated

granules should be mixed with milk, slightly acidic soft food or liquid such as apple juice, and then swallowed immediately without chewing. Any left-over food or liquid containing pancreatin should be discarded. Since pancreatin is also inactivated by heat, excessive heat should be avoided if preparations are mixed with liquids or food.

Pancreatin can irritate the perioral skin and buccal mucosa if retained in the mouth, and excessive doses can cause perianal irritation. Hypersensitivity reactions may occur particularly if the powder is handled.

PANCREATIN

Cautions see notes above; hyperuricaemia and hyperuricosuria have been associated with very high doses; **interactions:** Appendix 1 (pancreatin)

Pregnancy not known to be harmful

Side-effects nausea, vomiting, abdominal discomfort; skin and mucosal irritation (see notes above)

Indications and dose

Pancreatic insufficiency for dose see individual preparations, below

Creon® 10 000 (Abbott Healthcare)

Capsules, brown/clear, enclosing buff-coloured e/c granules of pancreatin (pork), providing: protease 600 units, lipase 10 000 units, amylase 8000 units, net price 100-cap pack = £12.93. Counselling, see dose

Dose

- **By mouth**
Child 1 month–18 years initially 1–2 capsules with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing), see notes above

Creon® Micro (Abbott Healthcare)

Gastro-resistant granules, brown, pancreatin (pork), providing: protease 200 units, lipase 5000 units, amylase 3600 units per 100 mg, net price 20 g = £31.50. Counselling, see dose

Dose

- **By mouth**
Neonate initially 100 mg before each feed; granules can be mixed with a small amount of breast milk or formula feed and administered immediately (manufacturer recommends mixing with a small amount of apple juice before administration)
Child 1 month–18 years initially 100 mg before each feed or meal; granules can be mixed with a small amount of milk or soft food and administered immediately (manufacturer recommends mixing with acidic liquid or pureed fruit before administration); see notes above
Note 100 mg granules = one measured scoopful (scoop supplied with product). Granules should not be chewed before swallowing.

Pancrex® (Essential)

Granules, pancreatin (pork), providing minimum of: protease 300 units, lipase 5000 units, amylase 4000 units/g. Net price 300 g = £57.00. Label: 25, counselling, see dose

Excipients include lactose (7 g per 10 g dose)

Dose

- **By mouth**
Child 2–18 years 5–10 g just before meals washed down or mixed with milk or water

Pancrex V® (Essential)

Capsules, pancreatin (pork), providing minimum of: protease 430 units, lipase 8000 units, amylase 9000 units, net price 300-cap pack = £53.20. Counselling, see dose

Dose

● By mouth

Child 1 month–1 year contents of 1–2 capsules mixed with feeds

Child 1–18 years 2–6 capsules with meals, swallowed whole or sprinkled on food

Capsules '125', pancreatin (pork), providing minimum of: protease 160 units, lipase 2950 units, amylase 3300 units, net price 300-cap pack = £42.07.

Counselling, see dose

Dose

● By mouth

Neonate contents of 1–2 capsules in each feed (or mix with feed and give by spoon)

Tablets, e/c, pancreatin (pork), providing minimum of: protease 110 units, lipase 1900 units, amylase 1700 units, net price 300-tab pack = £38.79. Label: 5, 25, counselling, see dose

Dose

● By mouth

Child 2–18 years 5–15 tablets before meals

Tablets forte, e/c, pancreatin (pork), providing minimum of: protease 330 units, lipase 5600 units, amylase 5000 units, net price 300-tab pack = £48.11.

Label: 5, 25, counselling, see dose

Dose

● By mouth

Child 2–18 years 6–10 tablets before meals

Powder, pancreatin (pork), providing minimum of: protease 1400 units, lipase 25 000 units, amylase 30 000 units/g, net price 300 g = £58.88. Counselling, see dose

Dose

● By mouth

Neonate 250–500 mg with each feed

Child 1 month–18 years 0.5–2 g with meals, washed down or mixed with milk or water

Higher-strength preparations

See warning above

Counselling It is important to ensure adequate hydration at all times in children receiving higher-strength pancreatin preparations.

Creon® 25 000 (Abbott Healthcare) (PoM)

Capsules, orange/clear, enclosing brown-coloured e/c pellets of pancreatin (pork), providing: protease (total) 1000 units, lipase 25 000 units, amylase 18 000 units, net price 100-cap pack = £28.25.

Counselling, see above and under dose

Dose

● By mouth

Child 2–18 years initially 1–2 capsules with meals either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing), see notes above

Creon® 40 000 (Abbott Healthcare) (PoM)

Capsules, brown/clear, enclosing brown-coloured e/c granules of pancreatin (pork), providing: protease (total) 1600 units, lipase 40 000 units, amylase 25 000 units, net price 100-cap pack = £41.80. Counselling, see above and under dose

Dose

● By mouth

Child 2–18 years initially 1–2 capsules with meals either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing), see notes above

Nutrizym 22® (Merck Serono) (PoM)

Capsules, red/yellow, enclosing e/c minitablets of pancreatin (pork), providing minimum of: protease 1100 units, lipase 22 000 units, amylase 19 800 units, net price 100-cap pack = £33.33. Counselling, see above and under dose

Dose

● By mouth

Child 15–18 years 1–2 capsules with meals and 1 capsule with snacks, swallowed whole or contents taken with water or mixed with soft food (then swallowed immediately without chewing), see notes above

Pancrease HL® (Janssen) (PoM)

Capsules, enclosing light brown e/c minitablets of pancreatin (pork), providing minimum of: protease 1250 units, lipase 25 000 units, amylase 22 500 units. Net price 100 = £40.38. Counselling, see above and under dose

Dose

● By mouth

Child 15–18 years 1–2 capsules during each meal and 1 capsule with snacks swallowed whole or contents mixed with slightly acidic liquid or soft food (then swallowed immediately without chewing), see notes above

2 Cardiovascular system

2.1 Positive inotropic drugs	72	2.7.1 Inotropic sympathomimetics	108
2.1.1 Cardiac glycosides	72	2.7.2 Vasoconstrictor sympathomimetics	110
2.1.2 Phosphodiesterase type-3 inhibitors	74	2.7.3 Cardiopulmonary resuscitation	112
2.2 Diuretics	75	2.8 Anticoagulants and protamine	112
2.2.1 Thiazides and related diuretics	75	2.8.1 Parenteral anticoagulants	113
2.2.2 Loop diuretics	77	2.8.2 Oral anticoagulants	116
2.2.3 Potassium-sparing diuretics and aldosterone antagonists	79	2.8.3 Protamine sulfate	118
2.2.4 Potassium-sparing diuretics with other diuretics	80	2.9 Antiplatelet drugs	118
2.2.5 Osmotic diuretics	80	2.10 Myocardial infarction and fibrinolysis	120
2.2.6 Mercurial diuretics	81	2.10.1 Management of myocardial infarction	120
2.2.7 Carbonic anhydrase inhibitors	81	2.10.2 Fibrinolytic drugs	120
2.2.8 Diuretics with potassium	81	2.11 Antifibrinolytic drugs and haemostatics	121
2.3 Anti-arrhythmic drugs	81	2.12 Lipid-regulating drugs	123
2.3.1 Management of arrhythmias	81	2.13 Local sclerosants	129
2.3.2 Drugs for arrhythmias	81	2.14 Drugs affecting the ductus arteriosus	129
2.4 Beta-adrenoceptor blocking drugs	86		
2.5 Hypertension	90		
2.5.1 Vasodilator antihypertensive drugs and pulmonary hypertension	91		
2.5.1.1 Vasodilator antihypertensives	91		
2.5.1.2 Pulmonary hypertension	93		
2.5.2 Centrally acting antihypertensive drugs	96		
2.5.3 Adrenergic neurone blocking drugs	97		
2.5.4 Alpha-adrenoceptor blocking drugs	97		
2.5.5 Drugs affecting the renin-angiotensin system	98		
2.5.5.1 Angiotensin-converting enzyme inhibitors	98		
2.5.5.2 Angiotensin-II receptor antagonists	101		
2.6 Nitrates, calcium-channel blockers, and other antianginal drugs	103		
2.6.1 Nitrates	103		
2.6.2 Calcium-channel blockers	104		
2.6.3 Other antianginal drugs	108		
2.6.4 Peripheral vasodilators and related drugs	108		
2.7 Sympathomimetics	108		

This chapter also includes advice on the drug management of the following:

arrhythmias, p. 81
heart failure, p. 75
hypertension, p. 90
pulmonary hypertension, p. 93

2.1 Positive inotropic drugs

- 2.1.1 Cardiac glycosides
- 2.1.2 Phosphodiesterase type-3 inhibitors

Positive inotropic drugs increase the force of contraction of the myocardium. Drugs which produce inotropic effects include cardiac glycosides, phosphodiesterase inhibitors, and some sympathomimetics (section 2.7.1).

2.1.1 Cardiac glycosides

The cardiac glycoside digoxin increases the force of myocardial contraction and reduces conductivity within the atrioventricular (AV) node.

Digoxin is most useful in the treatment of supraventricular tachycardias, especially for controlling ventricular response in persistent atrial fibrillation (section 2.3.1). Digoxin has a limited role in children with chronic heart failure; for reference to the role of digoxin in heart failure, see section 2.2.

For the management of atrial fibrillation, the maintenance dose of digoxin is determined on the basis of the

ventricular rate at rest, which should not be allowed to fall below an acceptable level for the child.

Digoxin is now rarely used for rapid control of heart rate (see section 2.3.2), even with intravenous administration, response may take many hours; persistence of tachycardia is therefore not an indication for exceeding the recommended dose. The intramuscular route is **not** recommended.

In children with heart failure who are in sinus rhythm, a loading dose may not be required.

Unwanted effects depend both on the concentration of digoxin in the plasma and on the sensitivity of the conducting system or of the myocardium, which is often increased in heart disease. It can sometimes be difficult to distinguish between toxic effects and clinical deterioration because the symptoms of both are similar. The plasma-digoxin concentration alone cannot indicate toxicity reliably, but the likelihood of toxicity increases progressively through the range 1.5 to 3 micrograms/litre for digoxin. Renal function is very important in determining digoxin dosage.

Hypokalaemia predisposes the child to digitalis toxicity and should be avoided; it is managed by giving a potassium-sparing diuretic or, if necessary, potassium supplements.

If toxicity occurs, digoxin should be withdrawn; serious manifestations require urgent specialist management. **Digoxin-specific antibody fragments** are available for reversal of life-threatening overdosage (see Digoxin-specific Antibody, p. 74).

DIGOXIN

Cautions sick sinus syndrome; thyroid disease; hypoxia; severe respiratory disease; avoid hypokalaemia, hypomagnesaemia, hypercalcaemia, and hypoxia (risk of digitalis toxicity); monitor serum electrolytes and renal function; avoid rapid intravenous administration (risk of hypertension and reduced coronary flow); **interactions:** Appendix 1 (cardiac glycosides)

Contra-indications intermittent complete heart block, second degree AV block; supraventricular arrhythmias associated with accessory conducting pathways e.g. Wolff-Parkinson-White syndrome (although can be used in infancy); ventricular tachycardia or fibrillation; hypertrophic cardiomyopathy (unless concomitant atrial fibrillation and heart failure—but use with caution); myocarditis; constrictive pericarditis (unless to control atrial fibrillation or improve systolic dysfunction—but use with caution)

Renal impairment use half normal dose if estimated glomerular filtration rate is 10–50 mL/minute/ 1.73 m^2 and use a quarter normal dose if estimated glomerular filtration rate is less than 10 mL/minute/ 1.73 m^2 ; monitor plasma-digoxin concentration; toxicity increased by electrolyte disturbances

Pregnancy may need dosage adjustment

Breast-feeding amount too small to be harmful

Side-effects see notes above; also nausea, vomiting, diarrhoea; arrhythmias, conduction disturbances; dizziness; blurred or yellow vision; rash, eosinophilia; *less commonly* depression; *very rarely* anorexia, intestinal ischaemia and necrosis, psychosis, apathy, confusion, headache, fatigue, weakness, gynaecomastia on long-term use, and thrombocytopenia

Pharmacokinetics For plasma-digoxin concentration assay, blood should be taken at least 6 hours after a dose; plasma-digoxin concentration should be maintained in the range 0.8–2 micrograms/litre (see also notes above)

Licensed use heart failure, supraventricular arrhythmias

Indications and dose

Supraventricular arrhythmias and chronic heart failure (see also notes above) consult product literature for details

• By mouth

Neonate under 1.5 kg initially 25 micrograms/kg in 3 divided doses for 24 hours then 4–6 micrograms/kg daily in 1–2 divided doses

Neonate 1.5–2.5 kg initially 30 micrograms/kg in 3 divided doses for 24 hours then 4–6 micrograms/kg daily in 1–2 divided doses

Neonate over 2.5 kg initially 45 micrograms/kg in 3 divided doses for 24 hours then 10 micrograms/kg daily in 1–2 divided doses

Child 1 month–2 years initially 45 micrograms/kg in 3 divided doses for 24 hours then 10 micrograms/kg daily in 1–2 divided doses

Child 2–5 years initially 35 micrograms/kg in 3 divided doses for 24 hours then 10 micrograms/kg daily in 1–2 divided doses

Child 5–10 years initially 25 micrograms/kg (max. 750 micrograms) in 3 divided doses for 24 hours then 6 micrograms/kg daily (max. 250 micrograms daily) in 1–2 divided doses

Child 10–18 years initially 0.75–1.5 mg in 3 divided doses for 24 hours then 62.5–250 micrograms daily in 1–2 divided doses (higher doses may be necessary)

• By intravenous infusion (but rarely necessary)

Neonate under 1.5 kg initially 20 micrograms/kg in 3 divided doses for 24 hours then 4–6 micrograms/kg daily in 1–2 divided doses

Neonate 1.5–2.5 kg initially 30 micrograms/kg in 3 divided doses for 24 hours then 4–6 micrograms/kg daily in 1–2 divided doses

Neonate over 2.5 kg initially 35 micrograms/kg in 3 divided doses for 24 hours then 10 micrograms/kg daily in 1–2 divided doses

Child 1 month–2 years initially 35 micrograms/kg in 3 divided doses for 24 hours then 10 micrograms/kg daily in 1–2 divided doses

Child 2–5 years initially 35 micrograms/kg in 3 divided doses for 24 hours then 10 micrograms/kg daily in 1–2 divided doses

Child 5–10 years initially 25 micrograms/kg (max. 500 micrograms) in 3 divided doses for 24 hours then 6 micrograms/kg daily (max. 250 micrograms daily) in 1–2 divided doses

Child 10–18 years initially 0.5–1 mg in 3 divided doses for 24 hours then 62.5–250 micrograms daily in 1–2 divided doses (higher doses may be necessary)

Note The above doses may need to be reduced if digoxin (or another cardiac glycoside) has been given in the preceding 2 weeks. When switching from intravenous to oral route may need to increase dose by 20–33% to maintain the same plasma-digoxin concentration. For plasma concentration monitoring, blood should ideally be taken at least 6 hours after a dose

Administration for *intravenous infusion*, dilute with Sodium Chloride 0.9% or Glucose 5% to a max. concentration of 62.5 micrograms/mL; loading doses should be given over 30–60 minutes and maintenance dose over 10–20 minutes.

For *oral* administration, oral solution must **not** be diluted

Digoxin (Non-proprietary) (PoM)

Tablets, digoxin 62.5 micrograms, net price 28-tab pack = £1.28; 125 micrograms, 28-tab pack = 97p; 250 micrograms, 28-tab pack = 92p

Injection, digoxin 250 micrograms/mL, net price 2-mL amp = 70p

Excipients include alcohol, propylene glycol (see Excipients, p. 2)

Paediatric injection, digoxin 100 micrograms/mL Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Lanoxin® (Aspen) (PoM)

Tablets, digoxin 125 micrograms, net price 500-tab pack = £8.09; 250 micrograms (scored), 500-tab pack = £8.09

Injection, digoxin 250 micrograms/mL, net price 2-mL amp = 66p

Lanoxin-PG® (Aspen) (PoM)

Tablets, blue, digoxin 62.5 micrograms, net price 500-tab pack = £8.09

Elixir, yellow, digoxin 50 micrograms/mL. Do not dilute, measure with pipette. Net price 60 mL = £5.35. Counselling, use of pipette

Digoxin-specific antibody

Serious cases of digoxin toxicity should be discussed with the National Poisons Information Service, p. 23. **Digoxin-specific antibody fragments** are indicated for the treatment of known or strongly suspected life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine and when measures beyond the withdrawal of digoxin and correction of any electrolyte abnormalities are considered necessary (see also notes above).

DigiFab® (BTG) ▼ (PoM)

Intravenous infusion, powder for reconstitution, digoxin-specific antibody fragments (F(ab)), net price 40-mg vial = £750.00 (hosp. only)

Dose

Consult product literature

ENOXIMONE

Cautions heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction; monitor blood pressure, heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count, hepatic enzymes; avoid extravasation; **interactions:** Appendix 1 (phosphodiesterase type-3 inhibitors)

Hepatic impairment dose reduction may be required

Renal impairment consider dose reduction

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises caution—no information available

Side-effects ectopic beats; less frequently ventricular tachycardia or supraventricular arrhythmias (more likely in children with pre-existing arrhythmias); hypotension; also headache, insomnia, nausea and vomiting, diarrhoea; occasionally, chills, oliguria, fever, urinary retention; upper and lower limb pain

Licensed use not licensed for use in children

Indications and dose

Congestive heart failure, low cardiac output following cardiac surgery

- By intravenous injection and continuous intravenous infusion

Neonate initial loading dose of 500 micrograms/kg by *slow intravenous injection*, followed by 5–20 micrograms/kg/minute by *continuous intravenous infusion* over 24 hours adjusted according to response; max 24 mg/kg over 24 hours

Child 1 month–18 years initial loading dose of 500 micrograms/kg by *slow intravenous injection*, followed by 5–20 micrograms/kg/minute by *continuous intravenous infusion* over 24 hours adjusted according to response; max. 24 mg/kg over 24 hours

Administration for *intravenous administration*, dilute to concentration of 2.5 mg/mL with Sodium Chloride 0.9% or Water for Injections; the initial loading dose should be given by slow intravenous injection over at least 15 minutes. Use plastic apparatus—crystal formation if glass used

Perfan® (INCA-Pharm) (PoM)

Injection, enoximone 5 mg/mL. For dilution before use. Net price 20-mL amp = £15.02

Excipients include alcohol, propylene glycol (see Excipients, p. 2)

MILRINONE

Cautions see under Enoximone; also correct hypokalaemia; monitor renal function; **interactions:** Appendix 1 (phosphodiesterase type-3 inhibitors)

Contra-indications severe hypovolaemia

Renal impairment use half to three-quarters normal dose and monitor response if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—no information available

Side-effects ectopic beats, ventricular tachycardia, supraventricular arrhythmias (more likely in children with pre-existing arrhythmias), hypotension; head-

2.1.2 Phosphodiesterase type-3 inhibitors

Enoximone and **milrinone** are phosphodiesterase type-3 inhibitors that exert most of their effect on the myocardium. They possess positive inotropic and vasodilator activity and are useful in infants and children with low cardiac output especially after cardiac surgery. Phosphodiesterase type-3 inhibitors should be limited to short-term use because long-term oral administration has been associated with increased mortality in adults with congestive heart failure.

ache; *less commonly* ventricular fibrillation, chest pain, tremor, hypokalaemia, thrombocytopenia; *very rarely* bronchospasm, anaphylaxis, and rash

Licensed use not licensed for use in children under 18 years

Indications and dose

Congestive heart failure, low cardiac output following cardiac surgery, shock

• By intravenous infusion

Neonate initially 50–75 micrograms/kg over 30–60 minutes (reduce or omit initial dose if at risk of hypotension) then 30–45 micrograms/kg/hour by *continuous intravenous infusion* for 2–3 days (usually for 12 hours after cardiac surgery)

Child 1 month–18 years initially 50–75 micrograms/kg over 30–60 minutes (reduce or omit initial dose if at risk of hypotension) then 30–45 micrograms/kg/hour by *continuous intravenous infusion* for 2–3 days (usually for 12 hours after cardiac surgery)

Administration for *intravenous infusion* dilute with Glucose 5% or Sodium Chloride 0.9% or Sodium Chloride and Glucose intravenous infusion to a concentration of 200 micrograms/mL (higher concentrations of 400 micrograms/mL have been used); loading dose may be given undiluted if fluid-restricted

Primacor® (Sanofi-Aventis) (PmM)

Injection, milrinone (as lactate) 1 mg/mL, net price 10-mL amp = £19.91

2.2 Diuretics

- 2.2.1 **Thiazides and related diuretics**
- 2.2.2 **Loop diuretics**
- 2.2.3 **Potassium-sparing diuretics and aldosterone antagonists**
- 2.2.4 **Potassium-sparing diuretics with other diuretics**
- 2.2.5 **Osmotic diuretics**
- 2.2.6 **Mercurial diuretics**
- 2.2.7 **Carbonic anhydrase inhibitors**
- 2.2.8 **Diuretics with potassium**

Diuretics are used for a variety of conditions in children including pulmonary oedema (caused by conditions such as respiratory distress syndrome and bronchopulmonary dysplasia), congestive heart failure, and hypertension. Hypertension in children is often resistant to therapy and may require the use of several drugs in combination (see section 2.5). Maintenance of fluid and electrolyte balance can be difficult in children on diuretics, particularly neonates whose renal function may be immature.

Loop diuretics (section 2.2.2) are used for pulmonary oedema, congestive heart failure, and in renal disease.

Thiazides (section 2.2.1) are used less commonly than loop diuretics but are often used in combination with loop diuretics or spironolactone in the management of pulmonary oedema and, in lower doses, for hypertension associated with cardiac disease.

Aminophylline infusion has been used with intravenous furosemide to relieve fluid overload in critically ill children.

Heart failure Heart failure is less common in children than in adults; it can occur as a result of congenital heart disease (e.g. septal defects), dilated cardiomyopathy, myocarditis, or cardiac surgery. Drug treatment of heart failure due to left ventricular systolic dysfunction is covered below; optimal management of heart failure with preserved left ventricular function has not been established.

Acute heart failure can occur after cardiac surgery or as a complication in severe acute infections with or without myocarditis. Therapy consists of volume loading, vasodilator or inotropic drugs.

Chronic heart failure is initially treated with a **loop diuretic** (section 2.2.2), usually furosemide supplemented with **spironolactone**, **amilofruse**, or **potassium**.

If diuresis with furosemide is insufficient, the addition of **metolazone** or a **thiazide diuretic** (section 2.2.1) can be considered. With metolazone, the resulting diuresis can be profound and care is needed to avoid potentially dangerous electrolyte disturbance.

If diuretics are insufficient an ACE inhibitor, titrated to the maximum tolerated dose, can be used. **ACE inhibitors** (section 2.5.5.1) are used for the treatment of all grades of heart failure in adults and can also be useful for children with heart failure. Addition of **digoxin** (section 2.1.1) can be considered in children who remain symptomatic despite treatment with a diuretic and an ACE inhibitor.

Some beta-blockers improve outcome in adults with heart failure, but data on beta-blockers in children are limited. **Carvedilol** (section 2.4) has vasodilatory properties and therefore (like ACE inhibitors) also lowers afterload.

In children receiving specialist cardiology care, the phosphodiesterase type-3 inhibitor **enoximone** is sometimes used by mouth for its inotropic and vasodilator effects. Spironolactone (section 2.2.3) is usually used as a potassium-sparing drug with a loop diuretic; in adults low doses of spironolactone are effective in the treatment of heart failure. Careful monitoring of serum potassium is necessary if spironolactone is used in combination with an ACE inhibitor.

Potassium loss Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic.

Hypokalaemia is particularly dangerous in children being treated with cardiac glycosides. In hepatic failure hypokalaemia caused by diuretics can precipitate encephalopathy.

The use of potassium-sparing diuretics (section 2.2.3) avoids the need to take potassium supplements.

2.2.1 Thiazides and related diuretics

Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule. They are usually administered early in the day so that the diuresis does not interfere with sleep.

In the management of *hypertension* a low dose of a thiazide produces a maximal or near-maximal blood

pressure lowering effect, with very little biochemical disturbance. Higher doses cause more marked changes in plasma potassium, sodium, uric acid, glucose, and lipids, with little advantage in blood pressure control. For reference to the use of thiazides in chronic heart failure see section 2.2.

Bendroflumethiazide is licensed for use in children; **chlorthiazide** is also used.

Chlorthalidone, a thiazide-related compound, has a longer duration of action than the thiazides and may be given on alternate days in younger children.

Metolazone is particularly effective when combined with a loop diuretic (even in renal failure) and is most effective when given 30–60 minutes before furosemide; profound diuresis can occur and the child should therefore be monitored carefully.

Cautions See also section 2.2. Thiazides and related diuretics can exacerbate diabetes, gout, and systemic lupus erythematosus. Electrolytes should be monitored particularly with high doses, long-term use, or in renal impairment. Thiazides and related diuretics should also be used with caution in nephrotic syndrome, hyperaldosteronism, and malnourishment; **interactions:** Appendix 1 (diuretics).

Contra-indications Thiazides and related diuretics should be avoided in refractory hypokalaemia, hyponatraemia, and hypercalcaemia, symptomatic hyperuricaemia, and Addison's disease.

Hepatic impairment Thiazides and related diuretics should be used with caution in mild to moderate impairment and avoided in severe impairment. Hypokalaemia may precipitate coma, although hypokalaemia can be prevented by using a potassium-sparing diuretic.

Renal impairment Thiazides and related diuretics should be used with caution because they can further reduce renal function. They are ineffective if estimated glomerular filtration rate is less than 30 mL/minute/1.73 m² and should be avoided; metolazone remains effective but with a risk of excessive diuresis.

Pregnancy Thiazides and related diuretics should not be used to treat gestational hypertension. They may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may also be reduced. Stimulation of labour, uterine inertia, and meconium staining have also been reported.

Breast-feeding The amount of bendroflumethiazide, chlorthiazide, chlorthalidone, and metolazone present in milk is too small to be harmful; large doses may suppress lactation.

Side-effects Side-effects of thiazides and related diuretics include mild gastro-intestinal disturbances, postural hypotension, altered plasma-lipid concentrations, metabolic and electrolyte disturbances including hypokalaemia (see also notes above), hyponatraemia, hypomagnesaemia, hypercalcaemia, hyperglycaemia, hypochloraemic alkalosis, and hyperuricaemia, and gout. Less common side-effects include blood disorders including agranulocytosis, leucopenia and thrombocytopenia, and impotence. Pancreatitis, intrahepatic cholestasis, cardiac arrhythmias, headache, dizziness, paraesthesia, visual disturbances, and hypersensitivity reactions (including pneumonitis, pulmonary oedema,

photosensitivity, and severe skin reactions) have also been reported.

BENDROFLUMETHIAZIDE

(Bendrofluazide)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

Oedema in heart failure, renal disease, and hepatic disease; pulmonary oedema; hypertension

• By mouth

Child 1 month–2 years 50–100 micrograms/kg daily adjusted according to response

Child 2–12 years initially 50–400 micrograms/kg (max. 10 mg) daily then 50–100 micrograms/kg daily adjusted according to response (max. 10 mg daily)

Child 12–18 years initially 5–10 mg daily or on alternate days (2.5 mg daily in hypertension) as a single morning dose, adjusted according to response (max. 10 mg daily)

Bendroflumethiazide (Non-proprietary) (PoM)

Tablets, bendroflumethiazide 2.5 mg, net price 28-tab pack = 88p; 5 mg, 28-tab pack = 81p

Brands include *Aprinox*[®], *Neo-NaClex*[®]

CHLORTHAZIDE

Cautions see notes above; also neonate (theoretical risk of kernicterus if very jaundiced)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use not licensed

Indications and dose

Heart failure, hypertension, ascites

• By mouth

Neonate 10–20 mg/kg twice daily

Child 1–6 months 10–20 mg/kg twice daily

Child 6 months–12 years 10 mg/kg twice daily (max. 1 g daily)

Child 12–18 years 0.25–1 g once daily or 125–500 mg twice daily

Chronic hypoglycaemia section 6.1.4

Diabetes insipidus section 6.5.2

Preparations

Chlorthiazide oral suspension 250 mg/5 mL is available from 'special-order' manufacturers or specialist importing companies, see p. 840

CHLORTALIDONE

(Chlorthalidone)

Cautions see notes above**Contra-indications** see notes above**Hepatic impairment** see notes above**Renal impairment** see notes above**Pregnancy** see notes above**Breast-feeding** see notes above**Side-effects** see notes above; also *rarely* jaundice**Indications and dose****Hypertension**

• By mouth

Child 5–12 years 0.5–1 mg/kg in the morning every 48 hours; max. 1.7 mg/kg every 48 hours**Child 12–18 years** 25 mg daily in the morning, increased to 50 mg daily if necessary (but see notes above)**Stable heart failure**

• By mouth

Child 5–12 years 0.5–1 mg/kg in the morning every 48 hours; max. 1.7 mg/kg every 48 hours**Child 12–18 years** 25–50 mg daily in the morning, increased if necessary to 100–200 mg daily (reduce to lowest effective dose for maintenance)**Ascites, oedema in nephrotic syndrome**

• By mouth

Child 5–12 years 0.5–1 mg/kg in the morning every 48 hours; max. 1.7 mg/kg every 48 hours**Child 12–18 years** up to 50 mg daily**Hygroton®** (Alliance) (PoM)

Tablets, yellow, scored, chlortalidone 50 mg, net price 28-tab pack = £1.64

Note May be difficult to obtain**METOLAZONE****Cautions** see notes above; also acute porphyria (section 9.8.2)**Contra-indications** see notes above**Hepatic impairment** see notes above**Renal impairment** see notes above**Pregnancy** see notes above**Breast-feeding** see notes above**Side-effects** see notes above; also chills, chest pain**Licensed use** not licensed for use in children**Indications and dose****Oedema resistant to loop diuretics in heart failure, renal disease, and hepatic disease; pulmonary oedema; adjunct to loop diuretics to induce diuresis**

• By mouth

Child 1 month–12 years 100–200 micrograms/kg once or twice daily**Child 12–18 years** 5–10 mg once daily in the morning, increased to 5–10 mg twice daily in resistant oedema**Administration** tablets may be crushed and mixed with water immediately before use**Metolazone** (Non-Proprietary) (PoM)

Tablets, metolazone 2.5 mg and 5 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

2.2.2 Loop diuretics

Loop diuretics inhibit reabsorption of sodium, potassium, and chloride from the ascending limb of the loop of Henlé in the renal tubule and are powerful diuretics.

Furosemide and **bumetanide** are similar in activity; they produce dose-related diuresis. Furosemide is used extensively in children. It can be used for pulmonary oedema (e.g. in respiratory distress syndrome and bronchopulmonary dysplasia), congestive heart failure, and in renal disease.**Cautions** Hypovolaemia and hypotension should be corrected before initiation of treatment with loop diuretics; electrolytes should be monitored during treatment (see also Potassium Loss, section 2.2). Loop diuretics should be used with caution in comatose and precoma states associated with liver cirrhosis. Loop diuretics can exacerbate diabetes (but hyperglycaemia less likely than with thiazides) and gout; they can also cause acute urinary retention in children with obstruction of urinary outflow, therefore adequate urinary output should be established before initiating treatment.**Contra-indications** Loop diuretics should be avoided in severe hypokalaemia, severe hyponatraemia, anuria, and in renal failure due to nephrotoxic or hepatotoxic drugs.**Hepatic impairment** Hypokalaemia induced by loop diuretics may precipitate hepatic encephalopathy and coma—potassium-sparing diuretics can be used to prevent this.**Renal impairment** High doses of loop diuretics may occasionally be needed; high doses or rapid intravenous administration can cause tinnitus and deafness; high doses of bumetanide can also cause musculoskeletal pain.**Pregnancy** Furosemide and bumetanide should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition.**Side-effects** Side-effects of loop diuretics include mild gastro-intestinal disturbances, pancreatitis, hepatic encephalopathy, postural hypotension, temporary increase in serum-cholesterol and triglyceride concentration, hyperglycaemia (less common than with thiazides), acute urinary retention, electrolyte disturbances (including hyponatraemia, hypokalaemia (see section 2.2), increased calcium excretion (nephrocalcinosis and nephrolithiasis reported with long-term use of furosemide in preterm infants), hypochloraemia, and hypomagnesaemia), metabolic alkalosis, blood disorders (including bone marrow depression, thrombocytopenia, and leucopenia), hyperuricaemia, visual disturbances, tinnitus and deafness (usually with high doses and rapid intravenous administration, and in renal impairment), rash, and photosensitivity.**BUMETANIDE****Cautions** see notes above**Contra-indications** see notes above**Hepatic impairment** see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding no information available; may inhibit lactation

Side-effects see notes above; also gynaecomastia, breast pain, musculoskeletal pain (associated with high doses in renal failure)

Licensed use not licensed for use in children under 12 years

Indications and dose

Oedema in heart failure, renal disease, and hepatic disease; pulmonary oedema

• By mouth

Child 1 month–12 years 15–50 micrograms/kg 1–4 times daily (max. single dose 2 mg); do not exceed 5 mg daily

Child 12–18 years 1 mg in the morning, repeated after 6–8 hours if necessary; severe cases, 5 mg daily increased by 5 mg every 12–24 hours according to response

• By intravenous injection

Child 12–18 years 1–2 mg, repeated after 20 minutes if necessary

• By intravenous infusion over 30–60 minutes

Child 1 month–12 years 25–50 micrograms/kg

Child 12–18 years 1–5 mg

Administration for *intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%; concentrations above 25 micrograms/mL may cause precipitation

Bumetanide (Non-proprietary) (PoM)

Tablets, bumetanide 1 mg, net price 28-tab pack = £1.17; 5 mg, 28-tab pack = £6.83

Oral liquid, bumetanide 1 mg/5 mL, net price 150 mL = £128.00

Injection, bumetanide 500 micrograms/mL, net price 4-mL amp = £1.79

FUROSEMIDE (Frusemide)

Cautions see notes above; also hypoproteinaemia may reduce effect and increase risk of side-effects; hepatorenal syndrome; risk of ototoxicity may be reduced by giving high oral doses in 2 or more divided doses; effect may be prolonged in neonates; some liquid preparations contain alcohol, caution especially in neonates; **interactions:** Appendix 1 (diuretics)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above; also lower rate of infusion may be necessary

Pregnancy see notes above

Breast-feeding amount too small to be harmful; may inhibit lactation

Side-effects see notes above; also intrahepatic cholestasis and gout

Indications and dose

Oedema in heart failure, renal disease, and hepatic disease; pulmonary oedema

• By mouth

Neonate 0.5–2 mg/kg every 12–24 hours (every 24 hours if corrected gestational age under 31 weeks)

Child 1 month–12 years 0.5–2 mg/kg 2–3 times daily (every 24 hours if corrected gestational age

under 31 weeks); higher doses may be required in resistant oedema; max. 12 mg/kg daily, not to exceed 80 mg daily

Child 12–18 years 20–40 mg daily, increased in resistant oedema to 80–120 mg daily

• By slow intravenous injection

Neonate 0.5–1 mg/kg every 12–24 hours (every 24 hours if corrected gestational age under 31 weeks)

Child 1 month–12 years 0.5–1 mg/kg repeated every 8 hours as necessary; max. 2 mg/kg (max. 40 mg) every 8 hours

Child 12–18 years 20–40 mg repeated every 8 hours as necessary; higher doses may be required in resistant cases

• By continuous intravenous infusion

Child 1 month–18 years 0.1–2 mg/kg/hour (following cardiac surgery, initially 100 micrograms/kg/hour, doubled every 2 hours until urine output exceeds 1 mL/kg/hour)

Oliguria

• By mouth

Child 12–18 years initially 250 mg daily; if necessary, dose increased in steps of 250 mg given every 4–6 hours; max. single dose 2 g

• By intravenous infusion

Child 1 month–12 years 2–5 mg/kg up to 4 times daily (max. 1 g daily)

Child 12–18 years initially 250 mg over 1 hour, increase to 500 mg over 2 hours if satisfactory urine output not obtained, then give a further 1 g over 4 hours if no satisfactory response within subsequent hour, if no response obtained dialysis probably required; effective dose (up to 1 g, max. rate 4 mg/minute) can be repeated every 24 hours

Administration for administration by *mouth*, tablets can be crushed and mixed with water or injection solution diluted and given by mouth.

For *intravenous injection*, give over 5–10 minutes at a usual rate of 100 micrograms/kg/minute (not exceeding 500 micrograms/kg/minute), max. 4 mg/minute.

For *intravenous infusion*, dilute with Sodium Chloride 0.9% to a concentration of 1–2 mg/mL; glucose solutions unsuitable (infusion pH must be above 5.5)

Furosemide (Non-proprietary) (PoM)

Tablets, furosemide 20 mg, net price 28-tab pack = 82p; 40 mg, 28-tab pack = 78p; 500 mg, 28-tab pack = £18.04

Brands include Rusyde®

Oral solution, sugar-free, furosemide, net price 20 mg/5 mL, 150 mL = £14.36; 40 mg/5 mL, 150 mL = £18.54; 50 mg/5 mL, 150 mL = £20.03

Brands include Frusol® (contains alcohol 10%)

Injection, furosemide 10 mg/mL, net price 2-mL amp = 35p; 5-mL amp = 32p; 25-mL amp = £2.50

Lasix® (Sanofi-Aventis) (PoM)

Injection, furosemide 10 mg/mL, net price 2-mL amp = 75p

Note Large-volume furosemide injections also available; brands include Minijet®

2.2.3 Potassium-sparing diuretics and aldosterone antagonists

Spironolactone is the most commonly used potassium-sparing diuretic in children; it is an aldosterone antagonist and enhances potassium retention and sodium excretion in the distal tubule. Spironolactone is combined with other diuretics to reduce urinary potassium loss. It is also used in nephrotic syndrome, the long-term management of Bartter's syndrome, and high doses can help to control ascites in babies with chronic neonatal hepatitis. The clinical value of spironolactone in the management of pulmonary oedema in preterm neonates with chronic lung disease is uncertain.

Potassium canrenoate, given intravenously, is an alternative aldosterone antagonist that may be useful if a potassium-sparing diuretic is required and the child is unable to take oral medication. It is metabolised to canrenone, which is also a metabolite of spironolactone.

Amiloride on its own is a weak diuretic. It causes retention of potassium and is therefore given with thiazide or loop diuretics as an alternative to giving potassium supplements (see section 2.2.4 for compound preparations with thiazides or loop diuretics).

A potassium-sparing diuretic such as spironolactone or amiloride may also be used in the management of amphotericin-induced hypokalaemia.

Potassium supplements must **not** be given with potassium-sparing diuretics. Administration of a potassium-sparing diuretic to a child receiving an ACE inhibitor or an angiotensin-II receptor antagonist (section 2.5.5) can also cause severe hyperkalaemia.

AMILORIDE HYDROCHLORIDE

Cautions monitor electrolytes; diabetes mellitus; **interactions:** Appendix 1 (diuretics)

Contra-indications hyperkalaemia; anuria; Addison's disease

Renal impairment monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment); manufacturers advise avoid in severe impairment

Pregnancy not to be used for treating hypertension in pregnancy

Breast-feeding manufacturer advises avoid—no information available

Side-effects abdominal pain, gastro-intestinal bleeding, dry mouth, thirst, diarrhoea, constipation, anorexia, jaundice, dyspepsia, flatulence, vomiting, nausea, angina, arrhythmias, palpitation, postural hypotension, dyspnoea, cough, nasal congestion, confusion, headache, insomnia, weakness, tremor, agitation, dizziness, malaise, paraesthesia, encephalopathy, urinary disturbances, sexual dysfunction, hyperkalaemia, muscle cramp, arthralgia, visual disturbances, raised intra-ocular pressure, tinnitus, alopecia, pruritus, rash

Licensed use not licensed for use in children

Indications and dose

Adjunct to thiazide or loop diuretics for oedema in heart failure, and hepatic disease (where potassium conservation desirable)

• By mouth

Neonate 100–200 micrograms/kg twice daily

Child 1 month–12 years 100–200 micrograms/kg twice daily; max. 20 mg daily

Child 12–18 years 5–10 mg twice daily

Amiloride (Non-proprietary) (PoM)

Tablets, amiloride hydrochloride 5 mg, net price 28-tab pack = £4.16

Oral solution, sugar-free, amiloride hydrochloride 5 mg/5 mL, net price 150 mL = £39.73

Brands include Amilamont® (excipients include propylene glycol, see Excipients p. 2)

Compound preparations with thiazide or loop diuretics

See section 2.2.4

Aldosterone antagonists

SPIRONOLACTONE

Cautions potential metabolic products carcinogenic in rodents; monitor electrolytes (discontinue if hyperkalaemia); acute porphyria (section 9.8.2); **interactions:** Appendix 1 (diuretics)

Contra-indications hyperkalaemia; anuria; Addison's disease

Renal impairment monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment); avoid in acute renal insufficiency or severe impairment

Pregnancy use only if potential benefit outweighs risk—feminisation of male fetus in animal studies

Breast-feeding metabolites present in milk but amount probably too small to be harmful

Side-effects gastro-intestinal disturbances, hepatotoxicity, malaise, confusion, drowsiness, dizziness, gynaecomastia, benign breast tumour, breast pain, menstrual disturbances, changes in libido, hypertrichosis, electrolyte disturbances including hyperkalaemia (discontinue) and hyponatraemia, acute renal failure, hyperuricaemia, leucopenia, agranulocytosis, thrombocytopenia, leg cramps, alopecia, rash, Stevens-Johnson syndrome

Licensed use not licensed for reduction of hypokalaemia induced by diuretics or amphotericin

Indications and dose

Oedema in heart failure and in ascites, nephrotic syndrome, reduction of hypokalaemia induced by diuretics or amphotericin

• By mouth

Neonate 1–2 mg/kg daily in 1–2 divided doses; up to 7 mg/kg daily in resistant ascites

Child 1 month–12 years 1–3 mg/kg daily in 1–2 divided doses; up to 9 mg/kg daily in resistant ascites

Child 12–18 years 50–100 mg daily in 1–2 divided doses; up to 9 mg/kg daily (max. 400 mg daily) in resistant ascites

Spironolactone (Non-proprietary) (PoM)

Tablets, spironolactone 25 mg, net price 28 = £1.24; 50 mg, 28 = £1.64; 100 mg, 28 = £2.06. Label: 21

Oral suspensions, spironolactone 5 mg/5 mL, 10 mg/5 mL, 25 mg/5 mL, 50 mg/5 mL, and 100 mg/5 mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Aldactone® (Pharmacia) (PoM)

Tablets, f/c, spironolactone 25 mg (buff), net price 100-tab pack = £8.89; 50 mg (white), 100-tab pack = £17.78; 100 mg (buff), 28-tab pack = £9.96. Label: 21

POTASSIUM CANRENOATE

Cautions potential metabolic products carcinogenic in rodents; monitor electrolytes (discontinue if hyperkalaemia); hypotension; acute porphyria (section 9.8.2); **interactions**: Appendix 1 (diuretics)

Contra-indications hyperkalaemia; hyponatraemia

Renal impairment use with caution and monitor plasma-potassium concentration if estimated glomerular filtration rate 30–60 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy crosses placenta; feminisation and undescended testes in male fetus in animal studies—manufacturer advises avoid

Breast-feeding present in breast milk—manufacturer advises avoid

Side-effects drowsiness, headache, ataxia; menstrual irregularities; hyperuricaemia; pain at injection site on rapid administration; *less commonly* thrombocytopenia, eosinophilia, and hyperkalaemia; *rarely* hepatotoxicity, agranulocytosis, osteomalacia, hoarseness and deepening of voice, hypersensitivity reactions (including urticaria and erythema), and alopecia; also gastro-intestinal disturbances, hypotension, transient confusion with high doses, hyponatraemia, hypochloreaemic acidosis, mastalgia, gynaecomastia, and hirsutism

Licensed use not licensed for use in the UK

Indications and dose**Short-term diuresis for oedema in heart failure and in ascites**

- By intravenous injection over at least 3 minutes or intravenous infusion

Neonate 1–2 mg/kg twice daily

Child 1 month–12 years 1–2 mg/kg twice daily

Child 12–18 years 1–2 mg/kg (max. 200 mg) twice daily

Note To convert to equivalent oral spironolactone dose, multiply potassium canrenoate dose by 0.7

Administration consult product literature

Preparations

Potassium canrenoate injection is available from 'special-order' manufacturers or specialist importing companies, see p. 840

be justified in older children if compliance is a problem. The most commonly used preparations are listed below (but they may not be licensed for use in children—consult product literature), for other preparations see the BNF. For **interactions**, see Appendix 1 (diuretics).

Amiloride with thiazides**Co-amilofide** (Non-proprietary) (PoM)

Tablets, co-amilofide 2.5/25 (amiloride hydrochloride 2.5 mg, hydrochlorothiazide 25 mg), net price 28-tab pack = £5.64

Brands include *Moduret 25®*

Amiloride with loop diuretics**Co-amilofruse** (Non-proprietary) (PoM)

Tablets, co-amilofruse 2.5/20 (amiloride hydrochloride 2.5 mg, furosemide 20 mg). Net price 28-tab pack = 92p, 56-tab pack = £1.86

Brands include *Frumil LS®*

Tablets, co-amilofruse 5/40 (amiloride hydrochloride 5 mg, furosemide 40 mg). Net price 28-tab pack = £1.00, 56-tab pack = £2.16

Brands include *Frumil®*

Tablets, co-amilofruse 10/80 (amiloride hydrochloride 10 mg, furosemide 80 mg), net price 28-tab pack = £7.38

2.2.5 Osmotic diuretics

Mannitol is used to treat cerebral oedema, raised intra-ocular pressure, peripheral oedema, and ascites.

MANNITOL

Cautions extravasation causes inflammation and thrombophlebitis; monitor fluid and electrolyte balance, serum osmolality, and pulmonary and renal function; assess cardiac function before and during treatment; **interactions**: Appendix 1 (mannitol)

Contra-indications severe heart failure; severe pulmonary oedema; intracranial bleeding (except during craniotomy); anuria; severe dehydration

Renal impairment use with caution in severe impairment

Pregnancy manufacturer advises avoid unless essential—no information available

Breast-feeding manufacturer advises avoid unless essential—no information available

Side-effects *less commonly* hypotension, thrombophlebitis, fluid and electrolyte imbalance; *rarely* dry mouth, thirst, nausea, vomiting, oedema, raised intracranial pressure, arrhythmia, hypertension, pulmonary oedema, chest pain, headache, convulsions, dizziness, chills, fever, urinary retention, focal osmotic nephrosis, dehydration, cramp, blurred vision, rhinitis, skin necrosis, and hypersensitivity reactions (including urticaria and anaphylaxis); *very rarely* congestive heart failure and acute renal failure

Licensed use not licensed for use in children under 12 years

Indications and dose**Cerebral oedema, raised intra-ocular pressure**

- By intravenous infusion over 30–60 minutes

Child 1 month–12 years 0.25–1.5 g/kg repeated if necessary 1–2 times after 4–8 hours

Child 12–18 years 0.25–2 g/kg repeated if necessary 1–2 times after 4–8 hours

Although it is preferable to prescribe diuretics separately in children, the use of fixed combinations may

Peripheral oedema and ascites

- By intravenous infusion over 2–6 hours

Child 1 month–18 years 1–2 g/kg

Administration examine infusion for crystals; if crystals present, dissolve by warming infusion fluid (allow to cool to body temperature before administration); for mannitol 20%, an in-line filter is recommended (15-micron filters have been used)

Mannitol (Baxter) (PoM)

Intravenous infusion, mannitol 10%, net price 500-mL *Viaflo*® bag = £3.20; 20%, 250-mL *Viaflex*® bag = £3.78, 500-mL *Viaflex*® bag = £5.80

2.2.6 Mercurial diuretics

Classification not used in *BNF for Children*.

2.2.7 Carbonic anhydrase inhibitors

The carbonic anhydrase inhibitor **acetazolamide** is a weak diuretic although it is little used for its diuretic effect. Acetazolamide and eye drops of dorzolamide and brinzolamide inhibit the formation of aqueous humour and are used in glaucoma (section 11.6). In children, acetazolamide is also used in the treatment of epilepsy (section 4.8.1), and raised intracranial pressure (section 11.6).

2.2.8 Diuretics with potassium

Diuretics and potassium supplements should be prescribed separately for children.

2.3 Anti-arrhythmic drugs

2.3.1 Management of arrhythmias

2.3.2 Drugs for arrhythmias

2.3.1 Management of arrhythmias

Management of an arrhythmia requires precise diagnosis of the type of arrhythmia; electrocardiography and referral to a paediatric cardiologist is essential; underlying causes such as heart failure require appropriate treatment.

Arrhythmias may be broadly divided into bradycardias, supraventricular tachycardias, and ventricular arrhythmias.

Bradycardia Adrenaline (epinephrine) is useful in the treatment of symptomatic bradycardia in an infant or child.

Supraventricular tachycardias

In supraventricular tachycardia adenosine is given by rapid intravenous injection. If adenosine is ineffective, intravenous amiodarone, flecainide, or a beta-blocker (such as esmolol, see section 2.4) can be tried; verapamil can also be considered in children over 1 year. Atenolol, sotalol (section 2.4), and flecainide are used

for the prophylaxis of paroxysmal supraventricular tachycardias.

The use of d.c. shock and vagal stimulation also have a role in the treatment of supraventricular tachycardia.

Syndromes associated with accessory conducting pathways Amiodarone, flecainide, or a beta-blocker is used to prevent recurrence of supraventricular tachycardia in infants and young children with these syndromes (e.g. Wolff-Parkinson-White syndrome).

Atrial flutter In atrial flutter without structural heart defects, sinus rhythm is restored with d.c. shock or cardiac pacing; drug treatment is usually not necessary. Amiodarone is used in atrial flutter when structural heart defects are present or after heart surgery. Sotalol (section 2.4) may also be considered.

Atrial fibrillation Atrial fibrillation is very rare in children. To restore sinus rhythm d.c. shock is used; beta-blockers, alone or together with digoxin, may be useful for ventricular rate control.

Ectopic tachycardia Intravenous amiodarone is used in conjunction with body cooling and synchronised pacing in *postoperative* junctional ectopic tachycardia. Oral amiodarone or flecainide are used in *congenital* junctional ectopic tachycardia.

Amiodarone, flecainide, or a beta-blocker are used in atrial ectopic tachycardia; amiodarone is preferred in those with poor ventricular function.

Ventricular tachycardia and ventricular fibrillation

Pulseless ventricular tachycardia or ventricular fibrillation require resuscitation, see Paediatric Advanced Life Support algorithm (inside back cover). Amiodarone is used in resuscitation for pulseless ventricular tachycardia or ventricular fibrillation unresponsive to d.c. shock; lidocaine can be used as an alternative only if amiodarone is not available.

Amiodarone is also used in a haemodynamically stable child when drug treatment is required; lidocaine can be used as an alternative only if amiodarone is not available.

Torsade de pointes Torsade de pointes is a form of ventricular tachycardia associated with long QT syndrome, which may be congenital or drug induced. Episodes may be self-limiting, but are frequently recurrent and can cause impairment or loss of consciousness. If not controlled, the arrhythmia can progress to ventricular fibrillation and sometimes death. Intravenous magnesium sulfate (section 9.5.1.3) can be used to treat torsade de pointes (dose recommendations vary—consult local guidelines). Anti-arrhythmics can further prolong the QT interval, thus worsening the condition.

2.3.2 Drugs for arrhythmias

Anti-arrhythmic drugs can be classified clinically as those acting on supraventricular arrhythmias (adenosine, digoxin, and verapamil), those acting on both supraventricular and ventricular arrhythmias (amiodarone, beta-blockers, flecainide, and procainamide),

and those acting on ventricular arrhythmias (lidocaine). For the treatment of bradycardia, see section 2.3.1.

Anti-arrhythmic drugs can also be classified according to their effects on the electrical behaviour of myocardial cells during activity (the Vaughan Williams classification) although this classification is of less clinical significance:

Class I: membrane stabilising drugs (e.g. lidocaine, flecainide)

Class II: beta-blockers

Class III: amiodarone; sotalol (also Class II)

Class IV: calcium-channel blockers (includes verapamil but not dihydropyridines)

Cautions The negative inotropic effects of anti-arrhythmic drugs tend to be additive. Therefore special care should be taken if two or more are used, especially if myocardial function is impaired. Most drugs that are effective in countering arrhythmias can also provoke them in some circumstances; moreover, hypokalaemia enhances the arrhythmogenic (pro-arrhythmic) effect of many drugs.

Adenosine is the treatment of choice for terminating supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome). It is also used in the diagnosis of supraventricular arrhythmias. It is not negatively inotropic and does not cause significant hypotension. The injection should be administered by rapid intravenous injection into a central or large peripheral vein.

Amiodarone is useful in the management of both supraventricular and ventricular tachyarrhythmias. It can be given by intravenous infusion and by mouth, and causes little or no myocardial depression. Unlike oral amiodarone, intravenous amiodarone acts relatively rapidly. Intravenous amiodarone is also used in cardiopulmonary resuscitation for ventricular fibrillation or pulseless ventricular tachycardia unresponsive to d.c. shock (see algorithm, inside back cover).

Amiodarone has a very long half-life (extending to several weeks) and only needs to be given once daily (but high doses may cause nausea unless divided). Many weeks or months may be required to achieve steady-state plasma-amiodarone concentration; this is particularly important when drug interactions are likely (see also Appendix 1).

Most patients taking amiodarone develop corneal microdeposits (reversible on withdrawal of treatment); these rarely interfere with vision, but drivers may be dazzled by headlights at night. However, if vision is impaired or if optic neuritis or optic neuropathy occur, amiodarone must be stopped to prevent blindness and expert advice sought. Because of the possibility of phototoxic reactions, children and carers should be advised to shield the child's skin from light during treatment and for several months after discontinuing amiodarone; a wide-spectrum sunscreen (section 13.8.1) should be used to protect against both long-wave ultraviolet and visible light.

Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism can occur. Clinical assessment alone is unreliable, and laboratory tests should be performed before treatment and every 6 months. Thyroxine (T4) may be raised in the absence of hyperthyroidism; there-

fore tri-iodothyronine (T3), T4, and thyroid-stimulating hormone (thyrotrophin, TSH) should all be measured. A raised T3 and T4 with a very low or undetectable TSH concentration suggests the development of thyrotoxicosis. The thyrotoxicosis may be very refractory, and amiodarone should usually be withdrawn at least temporarily to help achieve control; treatment with carbimazole may be required. Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential; careful supervision is required.

Pneumonitis should always be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodarone. Fresh neurological symptoms should raise the possibility of peripheral neuropathy. Amiodarone is also associated with hepatotoxicity (see under amiodarone, below).

Beta-blockers act as anti-arrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart, for details see section 2.4. For special reference to the role of **sotalol** in ventricular arrhythmias, see section 2.4.

Oral administration of **digoxin** (section 2.1.1) slows the ventricular rate in atrial fibrillation and in atrial flutter. However, intravenous infusion of digoxin is rarely effective for rapid control of ventricular rate.

Flecainide is useful for the treatment of resistant re-entry supraventricular tachycardia, ventricular tachycardia, ventricular ectopic beats, arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome), and paroxysmal atrial fibrillation. Flecainide crosses the placenta and can be used to control fetal supraventricular arrhythmias.

Lidocaine can be used in cardiopulmonary resuscitation in children with ventricular fibrillation or pulseless ventricular tachycardia unresponsive to d.c. shock, but only if amiodarone is not available. Doses may need to be reduced in children with persistently poor cardiac output and hepatic or renal failure (see under lidocaine, below).

Verapamil (section 2.6.2) can cause severe haemodynamic compromise (refractory hypotension and cardiac arrest) when used for the acute treatment of arrhythmias in neonates and infants; it is contra-indicated in children under 1 year. It is also contra-indicated in those with congestive heart failure, syndromes associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome) and in most receiving concomitant beta-blockers. It can be useful in older children with supraventricular tachycardia.

ADENOSINE

Cautions monitor ECG and have resuscitation facilities available; atrial fibrillation or flutter with accessory pathway (conduction down anomalous pathway may increase); first degree AV block; bundle branch block; QT-interval prolongation; left main coronary artery stenosis; uncorrected hypovolaemia; stenotic valvular heart disease; left to right shunt; pericarditis; pericardial effusion; autonomic dysfunction; stenotic carotid artery disease with cerebrovascular insufficiency; recent myocardial infarction; severe heart failure; heart transplant (see dose); **interactions:**

Appendix 1 (adenosine)

Contra-indications second- or third-degree AV block and sick sinus syndrome (unless pacemaker fitted);

long QT syndrome; severe hypotension; decompensated heart failure; asthma

Pregnancy large doses may produce fetal toxicity; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding no information available—unlikely to be present in milk owing to short half-life

Side-effects nausea, arrhythmia (discontinue if asystole or severe bradycardia occur), sinus pause, AV block, flushing, angina (discontinue), dizziness, dyspnoea, headache, apprehension; *less commonly* metallic taste, palpitation, hyperventilation, weakness, blurred vision, sweating; *very rarely* transient worsening of intracranial hypertension, bronchospasm, injection-site reactions; *also reported* vomiting, syncope, hypotension (discontinue if severe), cardiac arrest, respiratory failure (discontinue), convulsions

Licensed use *Adenocor*® licensed for treatment of paroxysmal supraventricular tachycardia in children; not licensed for diagnosis in children; *Adenoscan*® not licensed in children

Indications and dose

Arrhythmias (see also section 2.3.1), diagnosis of arrhythmias

• By rapid intravenous injection

Neonates 150 micrograms/kg; if necessary repeat injection every 1–2 minutes increasing dose by 50–100 micrograms/kg until tachycardia terminated or max. single dose of 300 micrograms/kg given

Child 1 month–1 year 150 micrograms/kg; if necessary repeat injection every 1–2 minutes increasing the dose by 50–100 micrograms/kg until tachycardia terminated or max. single dose of 500 micrograms/kg given

Child 1–12 years 100 micrograms/kg; if necessary repeat injection every 1–2 minutes increasing dose by 50–100 micrograms/kg until tachycardia terminated or max. single dose of 500 micrograms/kg (max. 12 mg) given

Child 12–18 years initially 3 mg; if necessary followed by 6 mg after 1–2 minutes, and then by 12 mg after a further 1–2 minutes

Note In some children over 12 years 3-mg dose ineffective (e.g. if a small peripheral vein is used for administration) and higher initial dose sometimes used; however, those with heart transplant are **very sensitive** to the effects of adenosine, and should **not** receive higher initial doses. In children receiving dipyridamole reduce dose to a quarter of usual dose of adenosine

Administration by rapid intravenous injection over 2 seconds into central or large peripheral vein followed by rapid Sodium Chloride 0.9% flush; Injection solution may be diluted with Sodium Chloride 0.9% if required

Adenosine (Non-proprietary) (PoM)

Injection, adenosine 3 mg/mL, net price 2-mL vial = £4.45 (hosp. only)

Intravenous infusion, adenosine 3 mg/mL, net price 10-mL vial = £11.67 (hosp. only)

Adenocor® (Sanofi-Aventis) (PoM)

Injection, adenosine 3 mg/mL, net price 2-mL vial = £4.99 (hosp. only)

Electrolytes Na⁺ 0.15 mmol/mL

Adenoscan® (Sanofi-Aventis) (PoM)

Intravenous infusion, adenosine 3 mg/mL, net price 10-mL vial = £14.26 (hosp. only)

Electrolytes Na⁺ 0.15 mmol/mL

Note *Adenoscan*® may be used in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate—consult product literature

AMIODARONE HYDROCHLORIDE

Cautions liver-function and thyroid-function tests required before treatment and then every 6 months (see notes above for tests of thyroid function); hypokalaemia (measure serum-potassium concentration before treatment); pulmonary function tests and chest x-ray required before treatment; heart failure; severe bradycardia and conduction disturbances in excessive dosage; intravenous use may cause moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) or severe hepato-cellular toxicity (monitor transaminases closely); ECG monitoring and resuscitation facilities must be available during intravenous use; acute porphyria (section 9.8.2); avoid benzyl alcohol containing injections in neonates (see Exciipients, p. 2); extreme caution or avoid concomitant use of drugs that prolong QT interval; **interactions:** Appendix 1 (amiodarone)

Contra-indications except in cardiac arrest: sinus bradycardia, sino-atrial heart block; unless pacemaker fitted avoid in severe conduction disturbances or sinus node disease; thyroid dysfunction; iodine sensitivity; avoid *intravenous use* in severe respiratory failure, circulatory collapse, or severe arterial hypotension; avoid bolus injection in congestive heart failure or cardiomyopathy; avoid rapid loading after cardiac surgery

Pregnancy possible risk of neonatal goitre; use only if no alternative

Breast-feeding avoid; significant amount present in milk—risk of neonatal hypothyroidism from release of iodine

Side-effects nausea, vomiting, taste disturbances, raised serum transaminases (may require dose reduction or withdrawal if accompanied by acute liver disorders), jaundice; bradycardia (see Cautions); pulmonary toxicity (including pneumonitis and fibrosis); tremor, sleep disorders; hypothyroidism, hyperthyroidism; reversible corneal microdeposits (sometimes with night glare); phototoxicity, persistent slate-grey skin discoloration (see also notes above); *less commonly* onset or worsening of arrhythmia, conduction disturbances (see Cautions), peripheral neuropathy and myopathy (usually reversible on withdrawal); *very rarely* chronic liver disease including cirrhosis, sinus arrest, bronchospasm (in patients with severe respiratory failure), ataxia, benign intracranial hypertension, headache, vertigo, epididymo-orchitis, impotence, haemolytic or aplastic anaemia, thrombocytopenia, rash (including exfoliative dermatitis), hypersensitivity including vasculitis, alopecia, impaired vision due to optic neuritis or optic neuropathy (including blindness), anaphylaxis on rapid injection, also hypotension, respiratory distress syndrome, sweating, and hot flushes

Licensed use not licensed for use in children under 3 years

Indications and dose

Supraventricular and ventricular arrhythmias see notes above (initiated in hospital or under specialist supervision)

- By mouth

Neonate initially 5–10 mg/kg twice daily for 7–10 days, then reduced to maintenance dose of 5–10 mg/kg once daily

Child 1 month–12 years initially 5–10 mg/kg (max. 200 mg) twice daily for 7–10 days, then reduced to maintenance dose of 5–10 mg/kg once daily (max. 200 mg daily)

Child 12–18 years 200 mg 3 times daily for 1 week then 200 mg twice daily for 1 week then usually 200 mg daily adjusted according to response

- By intravenous infusion

Neonate initially 5 mg/kg over 30 minutes then 5 mg/kg over 30 minutes every 12–24 hours

Child 1 month–18 years initially 5–10 mg/kg over 20 minutes–2 hours then *by continuous infusion* 300 micrograms/kg/hour, increased according to response to max. 1.5 mg/kg/hour; do not exceed 1.2 g in 24 hours

Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation (see also section 2.3.1)

- By intravenous injection

Neonate 5 mg/kg over at least 3 minutes

Child 1 month–18 years 5 mg/kg (max. 300 mg) over at least 3 minutes

Administration intravenous administration via central venous catheter recommended if repeated or continuous infusion required, as infusion via peripheral veins may cause pain and inflammation.

For *intravenous infusion*, dilute to a concentration of not less than 600 micrograms/mL with Glucose 5%; incompatible with Sodium Chloride infusion; avoid equipment containing the plasticizer di-2-ethylhexphthalate (DEHP).

For administration *by mouth*, tablets may be crushed and dispersed in water; injection solution should **not** be given orally (irritant)

Amiodarone (Non-proprietary) [PoM]

Tablets, amiodarone hydrochloride 100 mg, net price 28-tab pack = £1.18; 200 mg, 28-tab pack = £1.63. Label: 11

Injection, amiodarone hydrochloride 30 mg/mL, net price 10-mL prefilled syringe = £13.50

Excipients may include benzyl alcohol (avoid in neonates unless no safer alternative available, see Excipients, p. 2)

Sterile concentrate, amiodarone hydrochloride 50 mg/mL, net price 3-mL amp = £1.33, 6-mL amp = £2.86. For dilution and use as an infusion

Excipients may include benzyl alcohol (avoid in neonates unless no safer alternative available, see Excipients, p. 2)

Cordarone X[®] (Sanofi-Aventis) [PoM]

Tablets, scored, amiodarone hydrochloride 100 mg, net price 28-tab pack = £4.28; 200 mg, 28-tab pack = £6.99. Label: 11

Sterile concentrate, amiodarone hydrochloride 50 mg/mL, net price 3-mL amp = £1.60. For dilution and use as an infusion

Excipients include benzyl alcohol (avoid in neonates unless no safer alternative available, see Excipients, p. 2)

FLECAINIDE ACETATE

Cautions children with pacemakers (especially those who may be pacemaker dependent because stimulation threshold may rise appreciably); atrial fibrillation following heart surgery; monitor ECG and have resuscitation facilities available during intravenous use; **interactions:** Appendix 1 (flecainide)

Contra-indications heart failure; abnormal left ventricular function; long-standing atrial fibrillation where conversion to sinus rhythm not attempted; haemodynamically significant valvular heart disease; avoid in sinus node dysfunction, atrial conduction defects, second-degree or greater AV block, bundle branch block or distal block unless pacing rescue available

Hepatic impairment avoid or reduce dose in severe impairment; monitor plasma concentration (see pharmacokinetics below)

Renal impairment reduce dose by 25–50% if estimated glomerular filtration rate less than 35 mL/minute/1.73 m² and monitor plasma-flecainide concentration (see pharmacokinetics below)

Pregnancy used in pregnancy to treat maternal and fetal arrhythmias in specialist centres; toxicity reported in *animal* studies; infant hyperbilirubinaemia also reported

Breast-feeding significant amount present in milk but not known to be harmful

Side-effects oedema, pro-arrhythmic effects; dyspnoea; dizziness, asthenia, fatigue, fever; visual disturbances; *rarely* pneumonitis, hallucinations, depression, confusion, amnesia, dyskinesia, convulsions, peripheral neuropathy; *also reported* gastrointestinal disturbances, anorexia, hepatic dysfunction, flushing, syncope, drowsiness, tremor, vertigo, headache, anxiety, insomnia, ataxia, paraesthesia, hypoaesthesia, anaemia, leucopenia, thrombocytopenia, corneal deposits, tinnitus, increased anti-nuclear antibodies, hypersensitivity reactions (including rash, urticaria, and photosensitivity), increased sweating

Pharmacokinetics plasma-flecainide concentration for optimal response 200–800 micrograms/litre; blood sample should be taken immediately before next dose

Licensed use not licensed for use in children under 12 years

Indications and dose

Resistant re-entry supraventricular tachycardia, ventricular ectopic beats or ventricular tachycardia, arrhythmias associated with accessory conduction pathways (e.g. Wolff-Parkinson-White syndrome), paroxysmal atrial fibrillation

- By mouth

Neonate 2 mg/kg 2–3 times daily adjusted according to response and plasma-flecainide concentration

Child 1 month–12 years 2 mg/kg 2–3 times daily adjusted according to response and plasma-flecainide concentration (max. 8 mg/kg/day or 300 mg daily)

Child 12–18 years initially 50–100 mg twice daily; max. 300 mg daily (max. 400 mg daily for ventricular arrhythmias in heavily built children)

- By slow intravenous injection or intravenous infusion

Neonate 1–2 mg/kg over 10–30 minutes; if necessary followed by continuous infusion at a rate of 100–250 micrograms/kg/hour until arrhythmia controlled; transfer to *oral* treatment as above

Child 1 month–12 years 2 mg/kg over 10–30 minutes; if necessary followed by continuous infusion at a rate of 100–250 micrograms/kg/hour until arrhythmia controlled (max. cumulative dose 600 mg in 24 hours); transfer to *oral* treatment as above

Child 12–18 years 2 mg/kg (max. 150 mg) over 10–30 minutes; if necessary followed by continuous infusion at a rate of 1.5 mg/kg/hour for 1 hour, then reduced to 100–250 micrograms/kg/hour until arrhythmia controlled (max. cumulative dose 600 mg in first 24 hours); transfer to *oral* treatment as above

Administration for administration by *mouth*, milk, infant formula, and dairy products may reduce absorption of flecainide—separate doses from feeds. Liquid has a local anaesthetic effect and should be given at least 30 minutes before or after food. Do not store liquid in refrigerator as precipitation occurs. For *intravenous administration*, give initial dose over 30 minutes in children with sustained ventricular tachycardia or cardiac failure.

Dilute injection using Glucose 5%; concentrations of more than 300 micrograms/mL are unstable in chloride-containing solutions

Flecainide (Non-proprietary) (PoM)

Tablets, flecainide acetate 50 mg, net price 60-tab pack = £3.28; 100 mg, 60-tab pack = £4.78

Liquid, available from 'special-order' manufacturers or specialist importing companies, see p. 840

Tambacor® (Meda) (PoM)

Tablets, flecainide acetate 50 mg, net price 60-tab pack = £11.57; 100 mg (scored), 60-tab pack = £16.53

Injection, flecainide acetate 10 mg/mL, net price 15-mL amp = £4.40

■ Modified release

Tambacor® XL (Meda) (PoM)

Capsules, m/r, grey/pink, flecainide acetate 200 mg, net price 30-cap pack = £14.77. Label: 25 Dose

Supraventricular arrhythmias

- By mouth

Child 12–18 years 200 mg once daily

Note Not to be used to control arrhythmias in acute situations; children stabilised on 200 mg daily of immediate-release flecainide may be transferred to *Tambacor® XL*

Contra-indications sino-atrial disorders, all grades of atrioventricular block, severe myocardial depression

Hepatic impairment caution—increased risk of side-effects

Renal impairment possible accumulation of lidocaine and active metabolite; caution in severe impairment

Pregnancy crosses the placenta but not known to be harmful in *animal* studies—use if benefit outweighs risk

Breast-feeding present in milk but amount too small to be harmful

Side-effects dizziness, paraesthesia, or drowsiness (particularly if injection too rapid); other CNS effects include confusion, respiratory depression and convulsions; hypotension and bradycardia (may lead to cardiac arrest); *rarely* hypersensitivity reactions including anaphylaxis

Licensed use not licensed for use in children under 1 year

Indications and dose

Ventricular arrhythmias, pulseless ventricular tachycardia or ventricular fibrillation

- By intravenous or intraosseous injection, and intravenous infusion

Neonate 0.5–1 mg/kg by injection followed by infusion of 0.6–3 mg/kg/hour; if infusion not immediately available following initial injection, injection of 0.5–1 mg/kg may be repeated at intervals of not less than 5 minutes (to max. total dose 3 mg/kg) until infusion can be initiated

Child 1 month–12 years 0.5–1 mg/kg by injection followed by infusion of 0.6–3 mg/kg/hour; if infusion not immediately available following initial injection, injection of 0.5–1 mg/kg may be repeated at intervals of not less than 5 minutes (to max. total dose 3 mg/kg) until infusion can be initiated

Child 12–18 years 50–100 mg by injection followed by infusion of 120 mg over 30 minutes then 240 mg over 2 hours then 60 mg/hour; reduce dose further if infusion continued beyond 24 hours; if infusion not immediately available following initial injection, injection of 50–100 mg may be repeated at intervals of not less than 5 minutes (to max. 300 mg in 1 hour) until infusion can be initiated

Neonatal seizures (section 4.8.1)

- By intravenous infusion

Neonate initially 2 mg/kg over 10 minutes, followed by 6 mg/kg/hour for 6 hours; reduce dose over the following 24 hours (4 mg/kg/hour for 12 hours, then 2 mg/kg/hour for 12 hours)

Note Preterm neonates may require lower doses

Eye section 11.7

Local anaesthesia section 15.2

Administration for *intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%

Lidocaine (Non-proprietary) (PoM)

Injection 1%, lidocaine hydrochloride 10 mg/mL, net price 2-mL amp = 28p; 5-mL amp = 27p; 10-mL amp = 42p; 20-mL amp = 83p

Injection 2%, lidocaine hydrochloride 20 mg/mL, net price 2-mL amp = 35p; 5-mL amp = 32p; 10-mL amp = 60p; 20-mL amp = 80p

LIDOCAINE HYDROCHLORIDE (Lignocaine hydrochloride)

Cautions lower doses in congestive heart failure and following cardiac surgery; monitor ECG; resuscitation facilities should be available; **interactions:** Appendix 1 (lidocaine)

Infusion, lidocaine hydrochloride 0.1% (1 mg/mL) and 0.2% (2 mg/mL) in glucose intravenous infusion 5%. 500-mL containers

Minijet® Lidocaine (UCB Pharma) [PoM]

Injection, lidocaine hydrochloride 1% (10 mg/mL), net price 10-mL disposable syringe = £8.48; 2% (20 mg/mL), 5-mL disposable syringe = £8.18

2.4 Beta-adrenoceptor blocking drugs

Beta-adrenoceptor blocking drugs (beta-blockers) block the beta-adrenoceptors in the heart, peripheral vasculature, bronchi, pancreas, and liver.

Many beta-blockers are available but experience in children is limited to the use of only a few.

Differences between beta-blockers may affect choice. The water-soluble beta-blockers, atenolol and sotalol, are less likely to enter the brain and may therefore cause less sleep disturbance and nightmares. Water-soluble beta-blockers are excreted by the kidneys and dosage reduction is often necessary in renal impairment.

Some beta-blockers, such as atenolol, have an intrinsically longer duration of action and need to be given only once daily. Carvedilol and labetalol are beta-blockers which have, in addition, an arteriolar vasodilating action and thus lower peripheral resistance. Although carvedilol and labetalol possess both alpha- and beta-blocking properties, these drugs have no important advantages over other beta-blockers in the treatment of hypertension.

Beta-blockers slow the heart and can depress the myocardium; they are contra-indicated in children with second- or third-degree heart block. Sotalol may prolong the QT interval, and it occasionally causes life-threatening ventricular arrhythmias (**important**: particular care is required to avoid hypokalaemia in children taking sotalol).

Beta-blockers can precipitate asthma and should usually be avoided in children with a history of asthma or bronchospasm. If there is no alternative, a child with well-controlled asthma can be treated for a co-existing condition (e.g. arrhythmia) with a cardioselective beta-blocker, which should be initiated with caution at a low dose by a specialist and the child monitored closely for adverse effects. Atenolol and metoprolol have less effect on the beta₂ (bronchial) receptors and are, therefore, relatively *cardioselective*, but they are not *cardiospecific*; they have a lesser effect on airways resistance but are not free of this side-effect.

Beta-blockers are also associated with fatigue, coldness of the extremities, and sleep disturbances with nightmares (may be less common with the water-soluble beta-blockers, see above).

Beta-blockers can affect carbohydrate metabolism causing hypoglycaemia or hyperglycaemia in children with or without diabetes; they can also interfere with metabolic and autonomic responses to hypoglycaemia thereby masking symptoms such as tachycardia. However, beta-blockers are not contra-indicated in diabetes, although the cardioselective beta-blockers (e.g. atenolol and metoprolol) may be preferred. Beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia.

Pregnancy Beta-blockers may cause intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia; the risk is greater in severe hypertension. The use of labetalol in maternal hypertension is not known to be harmful, except possibly in the first trimester. Information on the safety of carvedilol during pregnancy is lacking. If beta-blockers are used close to delivery, infants should be monitored for signs of beta-blockade (and alpha-blockade with labetalol or carvedilol). For the treatment of hypertension in pregnancy, see section 2.5.

Breast-feeding Infants should be monitored as there is a risk of possible toxicity due to beta-blockade (and alpha-blockade with labetalol or carvedilol), but the amount of most beta-blockers present in milk is too small to affect infants. Atenolol and sotalol are present in milk in greater amounts than other beta-blockers. The manufacturer of esmolol advises avoidance if breast-feeding.

Hypertension Beta-blockers are effective for reducing blood pressure (section 2.5), but their mode of action is not understood; they reduce cardiac output, alter baroreceptor reflex sensitivity, and block peripheral adrenoceptors. Some beta-blockers depress plasma renin secretion. It is possible that a central effect may also partly explain their mode of action. Blood pressure can usually be controlled with relatively few side-effects. In general the dose of beta-blocker does not have to be high.

Labetalol may be given intravenously for *hypertensive emergencies* in children (section 2.5); however, care is needed to avoid dangerous hypotension or beta-blockade, particularly in neonates. **Esmolol** is also used intravenously for the treatment of hypertension particularly in the peri-operative period.

Beta-blockers can be used to control the pulse rate in children with *phaeochromocytoma* (section 2.5.4). However, they should never be used alone as beta-blockade without concurrent alpha-blockade may lead to a hypertensive crisis; phenoxybenzamine should always be used together with the beta-blocker.

Arrhythmias In arrhythmias (section 2.3), beta-blockers act principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart. They can be used alone or in conjunction with digoxin to control the ventricular rate in *atrial fibrillation*. Beta-blockers are also useful in the management of *supraventricular tachycardias* and *ventricular tachycardias* particularly to prevent recurrence of the tachycardia.

Esmolol is a relatively cardioselective beta-blocker with a very short duration of action, used intravenously for the short-term treatment of supraventricular arrhythmias and sinus tachycardia, particularly in the peri-operative period.

Sotalol is a non-cardioselective beta-blocker with additional class III anti-arrhythmic activity. Atenolol and sotalol suppress ventricular ectopic beats and non-sustained ventricular tachycardia (section 2.3.1). However, the pro-arrhythmic effects of sotalol, particularly in children with sick sinus syndrome, may prolong the QT interval and induce torsade de pointes.

Heart failure Beta-blockers may produce benefit in heart failure by blocking sympathetic activity and the addition of a beta-blocker such as **carvedilol** to other treatment for heart failure may be beneficial. Treatment

should be initiated by those experienced in the management of heart failure (see section 2.2 for details on heart failure).

Thyrotoxicosis Beta-blockers are used in the management of *thyrotoxicosis* including neonatal thyrotoxicosis; **propranolol** can reverse clinical symptoms within 4 days. Beta-blockers are also used for the pre-operative preparation for thyroidectomy; the thyroid gland is rendered less vascular, thus facilitating surgery (section 6.2.2).

Other uses In tetralogy of Fallot, esmolol or propranolol may be given intravenously in the initial management of *cyanotic spells*; propranolol is given by mouth for preventing cyanotic spells. If a severe cyanotic spell in a child with congenital heart disease persists despite optimal use of 100% oxygen, propranolol is given by intravenous infusion (for dose, see below). If cyanosis is still present after 10 minutes, sodium bicarbonate intravenous infusion is given in a dose of 1 mmol/kg to correct acidosis (or dose calculated according to arterial blood gas results); sodium bicarbonate 4.2% intravenous infusion is appropriate for a child under 1 year and sodium bicarbonate 8.4% intravenous infusion in children over 1 year. If blood-glucose concentration is less than 3 mmol/litre, glucose 10% intravenous infusion is given in a dose of 2 mL/kg (glucose 200 mg/kg) over 10 minutes, followed by morphine in a dose of 100 micrograms/kg by intravenous or intramuscular injection.

Beta-blockers are also used in the *prophylaxis of migraine* (section 4.7.4.2). Betaxolol, carteolol, levobunolol, and timolol are used topically in *glaucoma* (section 11.6).

PROPRANOLOL HYDROCHLORIDE

Cautions see notes above; also avoid abrupt withdrawal; first-degree AV block; portal hypertension (risk of deterioration in liver function); diabetes (see also notes above); history of obstructive airways disease (introduce cautiously and monitor lung function—see also notes above); myasthenia gravis; symptoms of thyrotoxicosis may be masked (see also notes above); psoriasis; history of hypersensitivity—may increase sensitivity to allergens and result in more serious hypersensitivity response, also may reduce response to adrenaline (epinephrine); **interactions:** Appendix 1 (beta-blockers), **important:** verapamil interaction, see also p. 107

Contra-indications asthma (but see notes above), uncontrolled heart failure, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; phaeochromocytoma (apart from specific use with alpha-blockers, see also notes above)

Bronchospasm Beta-blockers, including those considered to be cardioselective, should usually be avoided in children with a history of asthma or bronchospasm. However, where there is no alternative a cardioselective beta-blocker can be given with caution under specialist supervision

Hepatic impairment reduce oral dose

Renal impairment manufacturer advises caution—dose reduction may be required

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also gastro-intestinal disturbances; bradycardia, heart failure, hypotension, conduction disorders, peripheral vasoconstriction

(including exacerbation of intermittent claudication and Raynaud's phenomenon); bronchospasm (see above), dyspnoea; headache, fatigue, sleep disturbances, paraesthesia, dizziness, psychoses; sexual dysfunction; purpura, thrombocytopenia; visual disturbances; exacerbation of psoriasis, alopecia; *rarely* rashes and dry eyes (reversible on withdrawal); **overdosage:** see Emergency Treatment of Poisoning, p. 29

Licensed use not licensed for treatment of hypertension in children under 12 years

Indications and dose

Arrhythmias

• By mouth

Neonate 250–500 micrograms/kg 3 times daily, adjusted according to response

Child 1 month–18 years 250–500 micrograms/kg 3–4 times daily, adjusted according to response; max. 1 mg/kg 4 times daily, total daily dose not to exceed 160 mg daily

• By slow intravenous injection, with ECG monitoring

Neonate 20–50 micrograms/kg repeated if necessary every 6–8 hours

Child 1 month–18 years 25–50 micrograms/kg repeated every 6–8 hours if necessary

Hypertension

• By mouth

Neonate initially 250 micrograms/kg 3 times daily, increased if necessary to max. 2 mg/kg 3 times daily

Child 1 month–12 years 0.25–1 mg/kg 3 times daily, increased at weekly intervals to max. 5 mg/kg daily in divided doses

Child 12–18 years initially 80 mg twice daily; increased at weekly intervals as required; maintenance 160–320 mg daily; slow-release preparations may be used for once daily administration

Tetralogy of Fallot

• By mouth

Neonate 0.25–1 mg/kg 2–3 times daily, max. 2 mg/kg 3 times daily

Child 1 month–12 years 0.25–1 mg/kg 3–4 times daily, max. 5 mg/kg daily in divided doses

• By slow intravenous injection with ECG monitoring

Neonate initially 15–20 micrograms/kg (max. 100 micrograms/kg), repeated every 12 hours if necessary

Child 1 month–12 years initially 15–20 micrograms/kg (max. 100 micrograms/kg), repeated every 6–8 hours if necessary; higher doses rarely necessary

Migraine prophylaxis

• By mouth

Child 2–12 years initially 200–500 micrograms/kg twice daily; usual dose 10–20 mg twice daily; max. 2 mg/kg twice daily

Child 12–18 years initially 20–40 mg twice daily; usual dose 40–80 mg twice daily; max. 2 mg/kg (max. 120 mg) twice daily

Administration for *slow intravenous injection*, give over at least 3–5 minutes; rate of administration should not exceed 1 mg/minute. May be diluted with Sodium Chloride 0.9% or Glucose 5%. Incompatible with bicarbonate.

Note Excessive bradycardia can be countered with intravenous injection of atropine sulfate; for **overdosage** see Emergency Treatment of Poisoning, p. 29

Propranolol (Non-proprietary) (PoM)

Tablets, propranolol hydrochloride 10 mg, net price 28-tab pack = £3.15; 40 mg, 28-tab pack = £2.98; 80 mg, 56-tab pack = £3.24; 160 mg, 56-tab pack = £6.01. Label: 8

Brands include *Angilol*®

Oral solution, propranolol hydrochloride 5 mg/5 mL, net price 150 mL = £12.50; 10 mg/5 mL, 150 mL = £16.45; 40 mg/5 mL, 150 mL = £31.50; 50 mg/5 mL, 150 mL = £19.98. Label: 8

Brands include *Sypral*®

Injection, propranolol hydrochloride 1 mg/mL. Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Modified release

Note Modified-release preparations for once daily administration; use in older children only

Propranolol m/r preparations (PoM)

Capsules, m/r, propranolol hydrochloride 80 mg. Label: 8, 25

Brands include *Bedranol SR*®, *Half-Beta-Prograne*®

Capsules, m/r, propranolol hydrochloride 160 mg. Label: 8, 25

Brands include *Bedranol SR*®, *Beta-Prograne*®, *Slo-Pro*®

ATENOLOL

Cautions see under Propranolol Hydrochloride

Contra-indications see under Propranolol Hydrochloride

Renal impairment initially use 50% of usual dose if estimated glomerular filtration rate 10–35 mL/minute/1.73 m²; initially use 30–50% of usual dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride

Licensed use not licensed for use in children under 12 years

Indications and dose

Hypertension

• By mouth

Neonate 0.5–2 mg/kg once daily; may be given in 2 divided doses

Child 1 month–12 years 0.5–2 mg/kg once daily (doses higher than 50 mg daily rarely necessary); may be given in 2 divided doses

Child 12–18 years 25–50 mg once daily (higher doses rarely necessary); may be given in 2 divided doses

Arrhythmias

• By mouth

Neonate 0.5–2 mg/kg once daily; may be given in 2 divided doses

Child 1 month–12 years 0.5–2 mg/kg once daily (max. 100 mg daily); may be given in 2 divided doses

Child 12–18 years 50–100 mg once daily; may be given in 2 divided doses

Atenolol (Non-proprietary) (PoM)

Tablets, atenolol 25 mg, net price 28-tab pack = 98p; 50 mg, 28-tab pack = £1.03; 100 mg, 28-tab pack = £1.09. Label: 8

Tenormin® (AstraZeneca) (PoM)

LS tablets, orange, f/c, scored, atenolol 50 mg, net price 28-tab pack = £5.11. Label: 8

Tablets, orange, f/c, scored, atenolol 100 mg, net price 28-tab pack = £6.49. Label: 8

Syrup, sugar-free, atenolol 25 mg/5 mL, net price 300 mL = £13.55. Label: 8

CARVEDILOL

Cautions see under Propranolol Hydrochloride; monitor renal function during dose titration in children with heart failure who also have low blood pressure, renal impairment, ischaemic heart disease, or diffuse vascular disease

Contra-indications see under Propranolol Hydrochloride; acute or decompensated heart failure requiring intravenous inotropes

Hepatic impairment avoid

Pregnancy see notes above

Breast-feeding see notes above

Side-effects postural hypotension, dizziness, headache, fatigue, gastro-intestinal disturbances, bradycardia; occasionally diminished peripheral circulation, peripheral oedema and painful extremities, dry mouth, dry eyes, eye irritation or disturbed vision, impotence, disturbances of micturition, influenza-like symptoms; rarely angina, AV block, exacerbation of intermittent claudication or Raynaud's phenomenon; allergic skin reactions, exacerbation of psoriasis, nasal stuffiness, wheezing, depressed mood, sleep disturbances, paraesthesia, heart failure, changes in liver enzymes, thrombocytopenia, leucopenia also reported

Licensed use not licensed for use in children under 18 years

Indications and dose

Adjunct in heart failure (limited information available)

• By mouth

Child 2–18 years initially 50 micrograms/kg (max. 3.125 mg) twice daily, double dose at intervals of at least 2 weeks up to 350 micrograms/kg (max. 25 mg) twice daily

Carvedilol (Non-proprietary) (PoM)

Tablets, carvedilol 3.125 mg, net price 28-tab pack = £1.27; 6.25 mg, 28-tab pack = £1.46; 12.5 mg, 28-tab pack = £1.23; 25 mg, 28-tab pack = 94p. Label: 8

ESMOLOL HYDROCHLORIDE

Cautions see under Propranolol Hydrochloride

Contra-indications see under Propranolol Hydrochloride

Renal impairment manufacturer advises caution

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride; infusion causes venous irritation and thrombophlebitis

Licensed use not licensed for use in children

Indications and dose

Arrhythmias, hypertensive emergencies (see also notes above and section 2.5)

• By intravenous administration

Child 1 month–18 years initially by *intravenous injection* over 1 minute 500 micrograms/kg then by *intravenous infusion* 50 micrograms/kg/minute for 4 minutes (rate reduced if low blood pressure or low heart rate); if inadequate response, repeat loading dose and increase maintenance infusion by 50 micrograms/kg/minute increments; repeat until effective or max. infusion of 200 micrograms/kg/minute reached; doses over 300 micrograms/kg/minute not recommended

Tetralogy of Fallot

• By intravenous administration

Neonate initially by *intravenous injection* over 1–2 minutes 600 micrograms/kg then if necessary by *intravenous infusion* 300–900 micrograms/kg/minute

Administration give through a central venous catheter; incompatible with bicarbonate

Brevibloc® (Baxter) (PoM)

Injection, esmolol hydrochloride 10 mg/mL, net price 10-mL vial = £7.79, 250-mL infusion bag = £89.69

LABETALOL HYDROCHLORIDE

Cautions see under Propranolol Hydrochloride; interferes with laboratory tests for catecholamines; liver damage (see below)

Liver damage Severe hepatocellular damage reported after both short-term and long-term treatment. Appropriate laboratory testing needed at first symptom of liver dysfunction and if laboratory evidence of damage (or if jaundice) labetalol should be stopped and not restarted

Contra-indications see under Propranolol Hydrochloride

Renal impairment dose reduction may be required

Pregnancy see notes above

Breast-feeding see notes above

Side-effects postural hypotension (avoid upright position during and for 3 hours after intravenous administration), tiredness, weakness, headache, rashes, scalp tingling, difficulty in micturition, epigastric pain, nausea, vomiting; liver damage (see above); rarely lichenoid rash

Licensed use not licensed for use in children

Indications and dose

Hypertensive emergencies see also section 2.5

• By intravenous infusion

Neonate 500 micrograms/kg/hour adjusted at intervals of at least 15 minutes according to response; max. 4 mg/kg/hour

Child 1 month–12 years initially 0.5–1 mg/kg/hour adjusted at intervals of at least 15 minutes according to response; max. 3 mg/kg/hour

Child 12–18 years 30–120 mg/hour adjusted at intervals of at least 15 minutes according to response

Note Consult local guidelines. In hypertensive encephalopathy reduce blood pressure to normotensive level over 24–48 hours (more rapid reduction may lead to cerebral infarction, blindness, and death). If child fitting, reduce blood pressure rapidly, but not to normal levels

Hypertension

• By mouth

Child 1 month–12 years 1–2 mg/kg 3–4 times a day

Child 12–18 years initially 50–100 mg twice daily increased if required at intervals of 3–14 days to usual dose of 200–400 mg twice daily (3–4 divided doses if higher); max. 2.4 g daily

• By intravenous injection

Child 1 month–12 years 250–500 micrograms/kg as a single dose; max. 20 mg

Child 12–18 years 50 mg over at least 1 minute, repeated after 5 minutes if necessary; max. total dose 200 mg

Note Excessive bradycardia can be countered with intravenous injection of atropine sulfate; for **overdosage** see p. 29

Administration for *intravenous infusion*, dilute to a concentration of 1 mg/mL in Glucose 5% or Sodium Chloride and Glucose 5%; if fluid restricted may be given undiluted, preferably through a central venous catheter.

For administration *by mouth*, injection may be given orally with squash or juice

Labetalol Hydrochloride (Non-proprietary) (PoM)

Tablets, f/c, labetalol hydrochloride 100 mg, net price 56 = £5.88; 200 mg, 56 = £8.45; 400 mg, 56 = £23.03. Label: 8, 21

Injection, labetalol hydrochloride 5 mg/mL, net price 20-mL amp = £4.91

Trandate® (PharSafer) (PoM)

Tablets, all orange, f/c, labetalol hydrochloride 50 mg, net price 56-tab pack = £3.79; 100 mg, 56-tab pack = £4.64; 200 mg, 56-tab pack = £7.41; 400 mg, 56-tab pack = £10.15. Label: 8, 21

METOPROLOL TARTRATE

Cautions see under Propranolol Hydrochloride

Contra-indications see under Propranolol Hydrochloride

Hepatic impairment reduce dose in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride

Licensed use not licensed for use in children

Indications and dose

Hypertension

• By mouth

Child 1 month–12 years initially 1 mg/kg twice daily, increased if necessary to max. 8 mg/kg (max. 400 mg) daily in 2–4 divided doses

Child 12–18 years initially 50–100 mg daily increased if necessary to 200 mg daily in 1–2 divided doses; max. 400 mg daily (but high doses rarely necessary)

Arrhythmias

• By mouth

Child 12–18 years usually 50 mg 2–3 times daily; up to 300 mg daily in divided doses if necessary

Metoprolol Tartrate (Non-proprietary) (PoM)

Tablets, metoprolol tartrate 50 mg, net price 28-tab pack = 94p, 56-tab pack = £1.20; 100 mg, 28-tab pack = £1.03, 56-tab pack = £1.55. Label: 8

Lopresor® (Recordati) (PoM)

Tablets, f/c, scored, metoprolol tartrate 50 mg (pink), net price 56-tab pack = £2.57; 100 mg (blue), 56-tab pack = £6.68. Label: 8

Modified release

Lopresor SR® (Recordati) (PoM)

Tablets, m/r, yellow, f/c, metoprolol tartrate 200 mg, net price 28-tab pack = £9.80. Label: 8, 25 Dose

Hypertension

• By mouth

Child 12–18 years 200 mg once daily

SOTALOL HYDROCHLORIDE

Cautions see under Propranolol Hydrochloride; correct hypokalaemia, hypomagnesaemia, or other electrolyte disturbances; severe or prolonged diarrhoea; reduce dose or discontinue if corrected QT interval exceeds 550 msec; extreme caution or avoid concomitant use of drugs that prolong QT interval

Contra-indications see under Propranolol Hydrochloride; congenital or acquired long QT syndrome; torsade de pointes

Renal impairment halve normal dose if estimated glomerular filtration rate 30–60 mL/minute/1.73 m²; use one-quarter normal dose if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride; arrhythmogenic (pro-arrhythmic) effect (torsade de pointes—increased risk in females)

Licensed use not licensed for use in children under 12 years

Indications and dose

Ventricular arrhythmias, life-threatening ventricular tachyarrhythmia and supraventricular arrhythmias initiated under specialist supervision and ECG monitoring and measurement of corrected QT interval

• By mouth

Neonate initially 1 mg/kg twice daily, increased as necessary every 3–4 days to max. 4 mg/kg twice daily

Atrial flutter, ventricular arrhythmias, life-threatening ventricular tachyarrhythmia and supraventricular arrhythmias initiated under specialist supervision and ECG monitoring and measurement of corrected QT interval

• By mouth

Child 1 month–12 years initially 1 mg/kg twice daily, increased as necessary every 2–3 days to max. 4 mg/kg twice daily (max. 80 mg twice daily)

Child 12–18 years initially 80 mg once daily or 40 mg twice daily, increased gradually at intervals of 2–3 days to usual dose 80–160 mg twice daily; higher doses of 480–640 mg daily for life-threatening ventricular arrhythmias under specialist supervision

Administration for administration *by mouth*, tablets may be crushed and dispersed in water

Sotalol (Non-proprietary) (PoM)

Tablets, sotalol hydrochloride 40 mg, net price 28-tab pack = £1.38; 80 mg, 28-tab pack = £1.31; 160 mg, 28-tab pack = £5.71. Label: 8

Beta-Cardone® (PharSafer) (PoM)

Tablets, scored, sotalol hydrochloride 40 mg (green), net price 56-tab pack = £1.29; 80 mg (pink), 56-tab pack = £1.91; 200 mg, 28-tab pack = £2.40. Label: 8

Sotacor® (Bristol-Myers Squibb) (PoM)

Tablets, scored, sotalol hydrochloride 80 mg, net price 30-tab pack = £3.28. Label: 8

2.5 Hypertension

2.5.1 Vasodilator antihypertensive drugs and pulmonary hypertension

2.5.2 Centrally acting antihypertensive drugs

2.5.3 Adrenergic neurone blocking drugs

2.5.4 Alpha-adrenoceptor blocking drugs

2.5.5 Drugs affecting the renin-angiotensin system

Hypertension in children and adolescents can have a substantial effect on long-term health. Possible causes of hypertension (e.g. congenital heart disease, renal disease and endocrine disorders) and the presence of any complications (e.g. left ventricular hypertrophy) should be established. Treatment should take account of contributory factors and any factors that increase the risk of cardiovascular complications.

Serious hypertension is rare in *neonates* but it can present with signs of congestive heart failure; the cause is often renal and can follow embolic arterial damage.

Children (or their parents or carers) should be given advice on lifestyle changes to reduce blood pressure or

cardiovascular risk; these include weight reduction (in obese children), reduction of dietary salt, reduction of total and saturated fat, increasing exercise, increasing fruit and vegetable intake, and not smoking.

Indications for antihypertensive therapy in children include symptomatic hypertension, secondary hypertension, hypertensive target-organ damage, diabetes mellitus, persistent hypertension despite lifestyle measures (see above), and pulmonary hypertension (section 2.5.1.2). The effect of antihypertensive treatment on growth and development is not known; treatment should be started only if benefits are clear.

Antihypertensive therapy should be initiated with a single drug at the lowest recommended dose; the dose can be increased until the target blood pressure is achieved. Once the highest recommended dose is reached, or sooner if the patient begins to experience side-effects, a second drug may be added if blood pressure is not controlled. If more than one drug is required, these should be given as separate products to allow dose adjustment of individual drugs, but fixed-dose combination products may be useful in adolescents if compliance is a problem.

Acceptable drug classes for use in children with hypertension include **ACE inhibitors** (section 2.5.5.1), **alpha-blockers** (section 2.5.4), **beta-blockers** (section 2.4), **calcium-channel blockers** (section 2.6.2), and **thiazide diuretics** (section 2.2.1). There is limited information on the use of **angiotensin-II receptor antagonists** (section 2.5.5.2) in children. Diuretics and beta-blockers have a long history of safety and efficacy in children. The newer classes of antihypertensive drugs, including ACE inhibitors and calcium-channel blockers have been shown to be safe and effective in short-term studies in children. Refractory hypertension may require additional treatment with agents such as **minoxidil** (section 2.5.1.1) or **clonidine** (section 2.5.2).

Other measures to reduce cardiovascular risk

Aspirin (section 2.9) may be used to reduce the risk of cardiovascular events; however, concerns about an increased risk of bleeding and Reye's syndrome need to be considered.

A **statin** can be of benefit in older children who have a high risk of cardiovascular disease and have hypercholesterolaemia (see section 2.12).

Hypertension in diabetes Hypertension can occur in type 2 diabetes and treatment prevents both macrovascular and microvascular complications. ACE inhibitors (section 2.5.5.1) may be considered in children with diabetes and microalbuminaemia or proteinuric renal disease (see also section 6.1.5). Beta-blockers are best avoided in children with, or at a high risk of developing, diabetes, especially when combined with a thiazide diuretic.

Hypertension in renal disease ACE inhibitors may be considered in children with micro-albuminuria or proteinuric renal disease (see also section 6.1.5). High doses of loop diuretics may be required. Specific cautions apply to the use of ACE inhibitors in renal impairment, see section 2.5.5.1, but ACE inhibitors may be effective. Dihydropyridine calcium-channel blockers may be added.

Hypertension in pregnancy High blood pressure in pregnancy may usually be due to pre-existing essential hypertension or to pre-eclampsia. **Methyldopa** (BNF section 2.5.2) is safe in pregnancy. Beta-blockers

are effective and safe in the third trimester. Modified-release preparations of **nifedipine** [unlicensed] are also used for hypertension in pregnancy. Intravenous administration of **labetalol** (section 2.4) can be used to control hypertensive crises; alternatively **hydralazine** (section 2.5.1.1) can be given by the intravenous route.

Hypertensive emergencies Hypertensive emergencies in children may be accompanied by signs of hypertensive encephalopathy, including seizures. Controlled reduction in blood pressure over 72–96 hours is essential; rapid reduction can reduce perfusion leading to organ damage. Treatment should be initiated with intravenous drugs; once blood pressure is controlled, oral therapy can be started. It may be necessary to infuse fluids particularly during the first 12 hours to expand plasma volume should the blood pressure drop too rapidly.

Controlled reduction of blood pressure is achieved by intravenous administration of **labetalol** (section 2.4) or **sodium nitroprusside** (section 2.5.1.1). **Esmolol** (section 2.4) is useful for short-term use and has a short duration of action. **Nicardipine** (section 2.6.2) can be administered as a continuous intravenous infusion but it is not licensed for this use. In less severe cases, **nifedipine capsules** (section 2.6.2) can be used.

Other antihypertensive drugs which can be given intravenously include **hydralazine** (section 2.5.1.1) and **clonidine** (section 2.5.2).

Hypertension in acute nephritis occurs as a result of sodium and water retention; it should be treated with sodium and fluid restriction, and with furosemide (section 2.2.2); antihypertensive drugs may be added if necessary.

For advice on short-term management of hypertensive episodes in pheochromocytoma, see under Pheochromocytoma, section 2.5.4.

2.5.1 Vasodilator antihypertensive drugs and pulmonary hypertension

- 2.5.1.1 Vasodilator antihypertensives
- 2.5.1.2 Pulmonary hypertension

2.5.1.1 Vasodilator antihypertensives

Vasodilators have a potent hypotensive effect, especially when used in combination with a beta-blocker and a thiazide. **Important:** for a warning on the hazards of a very rapid fall in blood pressure, see Hypertensive Emergencies, above.

Sodium nitroprusside is given by intravenous infusion to control severe hypertensive crisis when parenteral treatment is necessary. At low doses it reduces systemic vascular resistance and increases cardiac output; at high doses it can produce profound systemic hypotension—continuous blood pressure monitoring is therefore essential. Sodium nitroprusside may also be used to control paradoxical hypertension after surgery for coarctation of the aorta.

Hydralazine is given by mouth as an adjunct to other antihypertensives for the treatment of resistant hypertension but is rarely used; when used alone it causes tachycardia and fluid retention. The incidence of side-

effects is lower if the dose is kept low, but systemic lupus erythematosus should be suspected if there is unexplained weight loss, arthritis, or any other unexplained ill health.

Minoxidil should be reserved for the treatment of severe hypertension resistant to other drugs. Vasodilation is accompanied by increased cardiac output and tachycardia and children develop fluid retention. For this reason the addition of a beta-blocker and a diuretic (usually furosemide, in high dosage) are mandatory. Hypertrichosis is troublesome and renders this drug unsuitable for females.

Prazosin and doxazosin (section 2.5.4) have alpha-blocking and vasodilator properties.

DIAZOXIDE

Cautions see section 6.1.4

Renal impairment see section 6.1.4

Pregnancy see section 6.1.4

Breast-feeding see section 6.1.4

Side-effects see section 6.1.4

Licensed use not licensed for resistant hypertension

Indications and dose

Resistant hypertension

• By mouth

Neonate initially 1.7 mg/kg 3 times daily, adjusted according to response; usual max. 15 mg/kg daily

Child 1 month–18 years initially 1.7 mg/kg 3 times daily, adjusted according to response; usual max. 15 mg/kg daily

Intractable hypoglycaemia section 6.1.4

Eudemine® (PharSafer) (PoM)

Tablets, see section 6.1.4

HYDRALAZINE HYDROCHLORIDE

Cautions cerebrovascular disease; occasionally blood pressure reduction too rapid even with low parenteral doses; manufacturer advises test for antinuclear factor and for proteinuria every 6 months and check acetylator status before increasing dose, but evidence of clinical value unsatisfactory; **interactions:** Appendix 1 (hydralazine)

Contra-indications idiopathic systemic lupus erythematosus, severe tachycardia, high output heart failure, myocardial insufficiency due to mechanical obstruction, cor pulmonale; acute porphyria (section 9.8.2)

Hepatic impairment reduce dose

Renal impairment reduce dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy neonatal thrombocytopenia reported, but risk should be balanced against risk of uncontrolled maternal hypertension; manufacturer advises avoid before third trimester

Breast-feeding present in milk but not known to be harmful; monitor infant

Side-effects tachycardia, palpitation, flushing, hypotension, fluid retention, gastro-intestinal disturbances; headache, dizziness; systemic lupus erythematosus-like syndrome after long-term therapy (especially in slow acetylators individuals); rarely rashes, fever, peripheral neuritis, polyneuritis, paraesthesia, arthralgia, myalgia, increased lacrimation, nasal congestion,

dyspnoea, agitation, anxiety, anorexia; blood disorders (including leucopenia, thrombocytopenia, haemolytic anaemia), abnormal liver function, jaundice, raised plasma creatinine, proteinuria and haematuria reported

Licensed use not licensed for use in children

Indications and dose

Hypertension

• By mouth

Neonate 250–500 micrograms/kg every 8–12 hours increased as necessary to max. 2–3 mg/kg every 8 hours

Child 1 month–12 years 250–500 micrograms/kg every 8–12 hours increased as necessary to max. 7.5 mg/kg daily (not exceeding 200 mg daily)

Child 12–18 years 25 mg twice daily, increased to usual max. 50–100 mg twice daily

• By slow intravenous injection

Neonate 100–500 micrograms/kg repeated every 4–6 hours as necessary; max. 3 mg/kg daily

Child 1 month–12 years 100–500 micrograms/kg repeated every 4–6 hours as necessary; max. 3 mg/kg daily (not exceeding 60 mg daily)

Child 12–18 years 5–10 mg repeated every 4–6 hours as necessary

• By continuous intravenous infusion (preferred route in cardiac patients)

Neonate 12.5–50 micrograms/kg/hour; max. 2 mg/kg daily

Child 1 month–12 years 12.5–50 micrograms/kg/hour; max. 3 mg/kg daily

Child 12–18 years 3–9 mg/hour; max. 3 mg/kg daily

Administration for intravenous injection, initially reconstitute 20 mg with 1 mL Water for Injections, then dilute to a concentration of 0.5–1 mg/mL with Sodium Chloride 0.9% and administer over 5–20 minutes.

For continuous intravenous infusion, initially reconstitute 20 mg with 1 mL Water for Injections, then dilute with Sodium Chloride 0.9%. Incompatible with Glucose intravenous infusion.

For administration *by mouth*, diluted injection may be given orally

Hydralazine (Non-proprietary) (PoM)

Tablets, hydralazine hydrochloride 25 mg, net price 56-tab pack = £8.94; 50 mg, 56-tab pack = £16.79

Apresoline® (AMCo) (PoM)

Tablets, yellow, s/c, hydralazine hydrochloride 25 mg, net price 84-tab pack = £3.38

Excipients include gluten, propylene glycol (see Excipients, p. 2)

Injection, powder for reconstitution, hydralazine hydrochloride, net price 20-mg amp = £2.22

MINOXIDIL

Cautions see notes above; acute porphyria (section 9.8.2); **interactions:** Appendix 1 (vasodilator antihypertensives)

Contra-indications phaeochromocytoma

Renal impairment use with caution in significant impairment

Pregnancy avoid—possible toxicity including reduced placental perfusion; neonatal hirsutism reported

Breast-feeding present in milk but not known to be harmful

Side-effects sodium and water retention; weight gain, peripheral oedema, tachycardia, hypertrichosis; reversible rise in creatinine and blood urea nitrogen; occasionally, gastro-intestinal disturbances, breast tenderness, rashes

Indications and dose

Severe hypertension

• By mouth

Child 1 month–12 years initially 200 micrograms/kg daily in 1–2 divided doses, increased in steps of 100–200 micrograms/kg daily at intervals of at least 3 days; max. 1 mg/kg daily

Child 12–18 years initially 5 mg daily in 1–2 divided doses increased in steps of 5–10 mg at intervals of at least 3 days; max. 100 mg daily (seldom necessary to exceed 50 mg daily)

Loniten® (Pharmacia) (POM)

Tablets, scored, minoxidil 2.5 mg, net price 60-tab pack = £8.88; 5 mg, 60-tab pack = £15.83; 10 mg, 60-tab pack = £30.68

SODIUM NITROPRUSSIDE

Cautions hypothyroidism, hyponatraemia, impaired cerebral circulation, hypothermia; monitor blood pressure and blood-cyanide concentration, and if treatment exceeds 3 days also blood-thiocyanate concentration; avoid sudden withdrawal—terminate infusion over 15–30 minutes; **interactions:** Appendix 1 (nitroprusside)

Contra-indications severe vitamin B₁₂ deficiency; Leber's optic atrophy; compensatory hypertension

Hepatic impairment use with caution; avoid in hepatic failure—cyanide or thiocyanate metabolites may accumulate

Renal impairment avoid prolonged use—cyanide or thiocyanate metabolites may accumulate

Pregnancy avoid prolonged use—potential for accumulation of cyanide in fetus

Breast-feeding no information available; caution advised due to thiocyanate metabolite

Side-effects associated with over rapid reduction in blood pressure (reduce infusion rate); headache, dizziness, nausea, retching, abdominal pain, perspiration, palpitation, anxiety, retrosternal discomfort; occasionally reduced platelet count, acute transient phlebitis

Cyanide Side-effects caused by excessive plasma concentration of the cyanide metabolite include tachycardia, sweating, hyperventilation, arrhythmias, marked metabolic acidosis (discontinue and give antidote, see p. 31)

Licensed use not licensed for use in the UK

Indications and dose

Hypertensive emergencies

• By continuous infusion

Neonate 500 nanograms/kg/minute then increased in steps of 200 nanograms/kg/minute as necessary to max. 8 micrograms/kg/minute (max. 4 micrograms/kg/minute if used for longer than 24 hours)

Child 1 month–18 years 500 nanograms/kg/minute then increased in steps of 200 nanograms/kg/minute as necessary to max. 8 micrograms/kg/minute (max. 4 micrograms/kg/minute if used for longer than 24 hours)

Administration for *continuous intravenous infusion* in Glucose 5%, infuse *via* infusion device to allow precise control; protect infusion from light. For further details, consult product literature

Sodium Nitroprusside (Non-proprietary) (POM)

Intravenous infusion, powder for reconstitution, sodium nitroprusside 10 mg/mL. For dilution and use as an infusion. Available from 'special-order' manufacturers or specialist importing companies, see p. 840

2.5.1.2 Pulmonary hypertension

Only pulmonary *arterial* hypertension is currently suitable for drug treatment. Pulmonary arterial hypertension includes persistent pulmonary hypertension of the newborn, idiopathic pulmonary arterial hypertension in children, and pulmonary hypertension related to congenital heart disease and cardiac surgery.

Some types of pulmonary hypertension are treated with vasodilator antihypertensive therapy and oxygen. Diuretics (section 2.2) may also have a role in children with right-sided heart failure.

Initial treatment of *persistent pulmonary hypertension of the newborn* involves the administration of **nitric oxide**; **epoprostenol** can be used until nitric oxide is available. Oral sildenafil may be helpful in less severe cases. Epoprostenol and sildenafil can cause profound systemic hypotension. In rare circumstances either **tolazoline** or **magnesium sulfate** can be given by intravenous infusion when nitric oxide and epoprostenol have failed.

Treatment of *idiopathic pulmonary arterial hypertension* is determined by acute vasodilator testing; drugs used for treatment include calcium-channel blockers (usually nifedipine, section 2.6.2), long-term intravenous **epoprostenol**, nebulised **iloprost**, **bosentan**, or **sildenafil**. Anticoagulation (usually with warfarin) may also be required to prevent secondary thrombosis.

Inhaled nitric oxide is a potent and selective pulmonary vasodilator. It acts on cyclic guanosine monophosphate (cGMP) resulting in smooth muscle relaxation. Inhaled nitric oxide is used in the treatment of persistent pulmonary hypertension of the newborn, and may also be useful in other forms of arterial pulmonary hypertension. Dependency can occur with high doses and prolonged use; to avoid rebound pulmonary hypertension the drug should be withdrawn gradually, often with the aid of sildenafil.

Excess nitric oxide can cause methaemoglobinaemia; therefore, methaemoglobin concentration should be measured regularly, particularly in neonates.

Nitric oxide increases the risk of haemorrhage by inhibiting platelet aggregation, but it does not usually cause bleeding.

Epoprostenol (prostacyclin) is a prostaglandin and a potent vasodilator. It is used in the treatment of persistent pulmonary hypertension of the newborn, idiopathic pulmonary arterial hypertension, and in the acute phase following cardiac surgery. It is given by continuous 24-hour intravenous infusion.

Epoprostenol is a powerful inhibitor of platelet aggregation and there is a possible risk of haemorrhage. It is sometimes used as an antiplatelet in renal dialysis when heparins are unsuitable or contra-indicated. It can also

cause serious systemic hypotension and, if withdrawn suddenly, can cause pulmonary hypertensive crisis.

Children on prolonged treatment can become tolerant to epoprostenol, and therefore require an increase in dose.

Iloprost is a synthetic analogue of epoprostenol and is efficacious when nebulised in adults with pulmonary arterial hypertension, but experience in children is limited. It is more stable than epoprostenol and has a longer half-life.

Bosentan is a dual endothelin receptor antagonist used orally in the treatment of pulmonary arterial hypertension. The concentration of endothelin, a potent vasoconstrictor, is raised in sustained pulmonary hypertension.

Sildenafil, a vasodilator developed for the treatment of erectile dysfunction, is also used for pulmonary arterial hypertension. It is used either alone or as an adjunct to other drugs.

Sildenafil is a selective phosphodiesterase type-5 inhibitor. Inhibition of this enzyme in the lungs enhances the vasodilatory effects of nitric oxide and promotes relaxation of vascular smooth muscle.

Sildenafil has also been used in pulmonary hypertension for weaning children off inhaled nitric oxide following cardiac surgery, and less successfully in idiopathic pulmonary arterial hypertension.

The *Scottish Medicines Consortium* (p. 3) has advised (October 2012) that sildenafil (*Revatio*[®]) is accepted for restricted use within NHS Scotland for the treatment of pulmonary arterial hypertension in children aged 1–17 years; sildenafil should only be prescribed on the advice of specialists in the Scottish Pulmonary Vascular Unit or the Scottish Adult Congenital Cardiac Service.

Tolazoline is now rarely used to correct pulmonary artery vasospasm in pulmonary hypertension of the newborn as better alternatives are available (see above). Tolazoline is an alpha-blocker and produces both pulmonary and systemic vasodilation.

BOSENTAN

Cautions not to be initiated if systemic systolic blood pressure is below 85 mmHg; monitor liver function before and at monthly intervals during treatment, and 2 weeks after dose increase (reduce dose or suspend treatment if liver enzymes raised significantly)—discontinue if symptoms of liver impairment (see Contra-indications below); monitor haemoglobin before and during treatment (monthly for first 4 months, then 3-monthly thereafter), withdraw treatment gradually; interactions: Appendix 1 (bosentan)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment avoid in moderate and severe impairment

Pregnancy avoid (teratogenic in *animal* studies); effective contraception required during administration (hormonal contraception not considered effective); monthly pregnancy tests advised

Breast-feeding manufacturer advises avoid—no information available

Side-effects diarrhoea, gastro-oesophageal reflux, flushing, hypotension, palpitation, oedema, syncope, headache, anaemia; *less commonly* thrombocytopenia, neutropenia, leucopenia; *rarely* liver cirrhosis, liver failure (see cautions above)

Indications and dose

Pulmonary arterial hypertension

• By mouth

Child 2–18 years and body-weight 10–20 kg initially 31.25 mg once daily increased after 4 weeks to 31.25 mg twice daily

Child 2–18 years and body-weight 20–40 kg initially 31.25 mg twice daily increased after 4 weeks to 62.5 mg twice daily

Child 12–18 years and body-weight over 40 kg initially 62.5 mg twice daily increased after 4 weeks to 125 mg twice daily; max. 250 mg twice daily

Administration tablets may be cut, or suspended in water or non-acidic liquid. Suspension is stable at room-temperature (max. 25°C) for 24 hours

Tracleer[®] (Actelion) (PoM)

Tablets, f/c, orange, bosentan (as monohydrate) 62.5 mg, net price 56-tab pack = £1510.21; 125 mg, 56-tab pack = £1510.21

EPOPROSTENOL

Cautions anticoagulant monitoring required when given with anticoagulants; haemorrhagic diathesis; concomitant use of drugs that increase risk of bleeding; monitor blood pressure; avoid abrupt withdrawal (risk of rebound pulmonary hypertension, see notes above)

Contra-indications severe left ventricular dysfunction; pulmonary veno-occlusive disease

Pregnancy manufacturer advises caution—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above; also nausea, vomiting, diarrhoea, abdominal pain, bleeding, bradycardia, tachycardia, flushing, chest pain, anxiety, headache, sepsis, jaw pain, arthralgia; *less commonly* dry mouth, pulmonary oedema, sweating; *rarely* agitation, pallor

Licensed use not licensed for use in children

Indications and dose

Persistent pulmonary hypertension of the newborn

• By continuous intravenous infusion

Neonate initially 2 nanograms/kg/minute adjusted according to response; usual max. 20 nanograms/kg/minute (rarely up to 40 nanograms/kg/minute)

Idiopathic pulmonary arterial hypertension

• By continuous intravenous infusion

Child 1 month–18 years initially 2 nanograms/kg/minute increased as necessary up to 40 nanograms/kg/minute

Administration reconstitute using the glycine buffer diluent provided to make a concentrate (pH 10.5); filter the concentrate using the filter provided. The concentrate can be administered via a central venous catheter, alternatively it may be diluted further either with the glycine buffer diluent or to a minimum concentration of 1.43 micrograms/mL with Sodium Chloride 0.9%. Solution stable for 12 hours at room temperature, although some units use for 24 hours and allow for loss of potency; solution stable for 24

hours if prepared in glycine buffer diluent only and administered via an ambulatory cold pouch system (to maintain solution at 2–8°C).

Neonatal intensive care, prepare a filtered concentrate of 10 micrograms/mL using the 500-microgram vial. **Neonate body-weight under 2 kg**, using the concentrate, dilute 150 micrograms/kg body-weight to a final volume of 50 mL with Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 nanograms/kg/minute. **Neonate body-weight over 2 kg**, using the concentrate, dilute 60 micrograms/kg body-weight to a final volume of 50 mL with Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 2 nanograms/kg/minute

Flolan® (GSK) (PoM)

Infusion, powder for reconstitution, epoprostenol (as sodium salt), net price 500-microgram vial (with diluent) = £22.22; 1.5-mg vial (▼) (with diluent) = £44.76

ILOPROST

Cautions unstable pulmonary hypertension with advanced right heart failure; hypotension (do not initiate if systolic blood pressure below 85 mmHg); acute pulmonary infection; severe asthma; *for inhaled treatment*, to minimise accidental exposure use only with nebulisers listed under *Ventavis®* preparation in a well ventilated room; **interactions**: Appendix 1 (iloprost)

Contra-indications decompensated cardiac failure (unless under medical supervision); severe coronary heart disease; severe arrhythmias; congenital or acquired valvular defects of the myocardium; pulmonary veno-occlusive disease; conditions which increase risk of haemorrhage

Hepatic impairment dose may need to be halved in liver cirrhosis—initially 2.5 micrograms at intervals of 3–4 hours (max. 6 times daily), adjusted according to response (consult product literature)

Pregnancy use if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, diarrhoea, oral irritation, haemorrhage, hypotension, chest pain, dyspnoea, cough, headache, throat or jaw pain, rash; *also reported* taste disturbance, bronchospasm, wheezing, thrombocytopenia

Licensed use not licensed for use in children under 18 years

Indications and dose

Idiopathic or familial pulmonary arterial hypertension

• By inhalation of nebulised solution

Child 8–18 years initial dose 2.5 micrograms increased to 5 micrograms for second dose, if tolerated maintain at 5 micrograms 6–9 times daily according to response; reduce to 2.5 micrograms 6–9 times daily if higher dose not tolerated

Raynaud's syndrome section 2.6.4.1

Ventavis® (Bayer) (PoM)

Nebuliser solution, iloprost (as trometamol) 10 micrograms/mL, net price 30 × 1-mL (10 microgram) unit-dose vials = £400.19, 168 × 1-mL = £2241.08. For use with *HaloLite®* (JMS), *I-Neb AAD®* (JMS), *Prodose®* (JMS), or *Venta-Neb®* (JMS) nebuliser

Note Delivery characteristics of nebuliser devices may vary—only switch devices under medical supervision

MAGNESIUM SULFATE

Note Magnesium Sulfate Injection BP is a sterile solution of Magnesium Sulfate Heptahydrate

Cautions see section 9.5.1.3

Hepatic impairment see section 9.5.1.3

Renal impairment see section 9.5.1.3

Side-effects see section 9.5.1.3

Indications and dose

Persistent pulmonary hypertension of the newborn

• By intravenous infusion

Neonate initially 200 mg/kg (0.8 mmol/kg Mg^{2+}) magnesium sulfate heptahydrate over 20–30 minutes; if response occurs, then by continuous intravenous infusion of 20–75 mg/kg/hour (0.08–0.3 mmol/kg/hour Mg^{2+}) (to maintain plasma-magnesium concentration between 3.5–5.5 mmol/litre), given for up to 5 days

Severe acute asthma section 3.1

Torsade de pointes section 9.5.1.3

Neonatal hypocalcaemia section 9.5.1.3

Hypomagnesaemia section 9.5.1.3

Administration for *intravenous infusion*, dilute to a max. concentration of 100 mg/mL (10%) (0.4 mmol/mL Mg^{2+}) magnesium sulfate heptahydrate (200 mg/mL (0.8 mmol/mL Mg^{2+}) if fluid restricted) with Glucose 5% or Sodium Chloride 0.9%

Note Magnesium sulfate heptahydrate 1 g equivalent to Mg^{2+} approx. 4 mmol

Magnesium Sulfate Injection, BP (Non-proprietary) (PoM)

Injection, magnesium sulfate heptahydrate 50% (Mg^{2+} approx. 2 mmol/mL), net price 2-mL (1-g) amp = 68p, 5-mL (2.5-g) amp = £3.00, 10-mL (5-g) amp = 68p; prefilled 10-mL (5-g) syringe = £4.95

Note The BP directs that the label states the strength as the % w/v of magnesium sulfate heptahydrate and as the approximate concentration of magnesium ions (Mg^{2+}) in mmol/mL

SILDENAFIL

Cautions hypotension (avoid if severe); intravascular volume depletion; left ventricular outflow obstruction; autonomic dysfunction; other cardiovascular disease; pulmonary veno-occlusive disease; predisposition to priapism; anatomical deformation of the penis; bleeding disorders or active peptic ulceration; ocular disorders; avoid abrupt withdrawal; initiate cautiously if child also on epoprostenol, iloprost, bosentan or nitric oxide; **interactions**: Appendix 1 (sildenafil)

Contra-indications recent history of stroke; history of non-arteritic anterior ischaemic optic neuropathy; hereditary degenerative retinal disorders; sickle-cell anaemia; avoid concomitant use of nitrates

Hepatic impairment reduce dose if not tolerated in mild to moderate impairment; manufacturer advises avoid in severe impairment

Renal impairment reduce dose if not tolerated

Pregnancy use only if potential benefit outweighs risk—no evidence of harm in *animal* studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects diarrhoea, dyspepsia, gastritis, abdominal distension, gastro-oesophageal reflux, haemorrhoids, dry mouth, flushing, oedema, bronchitis, cough, headache, migraine, night sweats, paraesthesia, insomnia, anxiety, tremor, vertigo, fever, influenza-like symptoms, anaemia, back and limb pain, myalgia, visual disturbances, retinal haemorrhage, photophobia, painful red eyes, nasal congestion, epistaxis, cellulitis, alopecia; *less commonly* gynaecomastia, priapism, haematuria, penile haemorrhage; *also reported* rash, retinal vascular occlusion, non-arteritic anterior ischaemic optic neuropathy (discontinue if sudden visual impairment occurs), and sudden hearing loss (advise patient to seek medical help)

Licensed use not licensed for use in children under 1 year

Indications and dose

Pulmonary arterial hypertension

- By mouth

Neonate initially 250–500 micrograms/kg every 4–8 hours, adjusted according to response; max. 30 mg daily; start with lower dose and frequency especially if used with other vasodilators (see Cautions above)

Child 1 month–1 year initially 250–500 micrograms/kg every 4–8 hours, adjusted according to response; max. 30 mg daily; start with lower dose and frequency especially if used with other vasodilators (see Cautions above)

Child 1–18 years

Body-weight under 20 kg 10 mg three times daily

Body-weight over 20 kg 20 mg three times daily

Revatio® (Pfizer) (PoM)

Tablets, f/c, sildenafil (as citrate), 20 mg, net price 90-tab pack = £446.33

Oral suspension, sildenafil (as citrate) 10 mg/mL when reconstituted with water, net price 112-mL = £186.75

TOLAZOLINE

Cautions mitral stenosis; cardiotoxic accumulation may occur with continuous infusion, particularly in renal impairment—monitor blood pressure regularly for sustained systemic hypotension; **interactions:** Appendix 1 (alpha-blockers)

Contra-indications peptic ulcer disease

Renal impairment accumulates in renal impairment; risk of cardiotoxicity; lower doses may be necessary

Side-effects nausea, vomiting, diarrhoea, epigastric pain; flushing, tachycardia, cardiac arrhythmias; headache, shivering, sweating; oliguria, metabolic alkalosis, haematuria, blood dyscrasias (including thrombocytopenia); blotchy skin; at high doses severe hypotension, marked hypertension, renal failure, and haemorrhage reported

Licensed use not licensed for use in children

Indications and dose

Correction of pulmonary vasospasm in neonates

- By intravenous injection and continuous intravenous infusion (maintenance)

Neonate initially 1 mg/kg by intravenous injection over 2–5 minutes, followed if necessary by continuous intravenous infusion of 200 micrograms/kg/hour with careful blood pressure monitoring; doses above 300 micrograms/kg/hour associated with cardiotoxicity and renal failure

- By endotracheal administration

Neonate 200 micrograms/kg

Administration for continuous intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%. Prepare a fresh solution every 24 hours.

For endotracheal administration, dilute with 0.5–1 mL of Sodium Chloride 0.9%

Tolazoline (Non-proprietary)

Injection, tolazoline 25 mg/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

2.5.2 Centrally acting antihypertensive drugs

Methyldopa, a centrally acting antihypertensive, is of little value in the management of refractory sustained hypertension in infants and children. On prolonged use it is associated with fluid retention (which may be alleviated by concomitant use of diuretics).

Methyldopa is effective for the management of hypertension in pregnancy (see BNF section 2.5.2).

Clonidine is also a centrally acting antihypertensive but has the disadvantage that sudden withdrawal may cause a hypertensive crisis. Clonidine is also used under specialist supervision for pain management, sedation, and opioid withdrawal, attention deficit hyperactivity disorder, and Tourette syndrome.

CLONIDINE HYDROCHLORIDE

Cautions must be withdrawn gradually to avoid hypertensive crisis; mild to moderate bradyarrhythmia; constipation; polyneuropathy; Raynaud's syndrome or other occlusive peripheral vascular disease; history of depression; **interactions:** Appendix 1 (clonidine)

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced

Contra-indications severe bradyarrhythmia secondary to second- or third-degree AV block or sick sinus syndrome

Renal impairment use with caution

Pregnancy may lower fetal heart rate, but risk should be balanced against risk of uncontrolled maternal hypertension; avoid intravenous injection

Breast-feeding avoid—present in milk

Side-effects constipation, nausea, dry mouth, vomiting, salivary gland pain, postural hypotension, dizziness, sleep disturbances, headache, malaise, drowsiness, depression, sexual dysfunction; *less commonly* bradycardia, Raynaud's syndrome, delusion, hallucination, paraesthesia, pruritus, rash, urticaria; *rarely* colonic pseudo-obstruction, AV block, gynaecomastia

tia, decreased lacrimation, nasal dryness, alopecia; *also reported* hepatitis, fluid retention, bradyarrhythmia, confusion, impaired visual accommodation

Licensed use not licensed for use in children

Indications and dose

Severe hypertension

• By mouth

Child 2–18 years initially 0.5–1 microgram/kg 3 times daily, increased gradually if necessary; max. 25 micrograms/kg daily in divided doses (not exceeding 1.2 mg daily)

• By slow intravenous injection

Child 2–18 years 2–6 micrograms/kg (max. 300 micrograms) as a single dose

Administration for intravenous injection, give over 10–15 minutes; compatible with Sodium Chloride 0.9% or Glucose 5%.

For administration *by mouth*, tablets may be crushed and dissolved in water

Catapres® (Boehringer Ingelheim) (PoM) 

Tablets, scored, clonidine hydrochloride 100 micrograms, net price 100-tab pack = £8.04. Label: 3, 8

Injection, clonidine hydrochloride 150 micrograms/mL, net price 1-mL amp = 42p

2.5.3 Adrenergic neurone blocking drugs

Adrenergic neurone blocking drugs prevent the release of noradrenaline from postganglionic adrenergic neurones. These drugs do not control supine blood pressure and may cause postural hypotension. For this reason they have largely fallen from use in adults and are rarely used in children.

2.5.4 Alpha-adrenoceptor blocking drugs

Doxazosin and prazosin have post-synaptic alpha-blocking and vasodilator properties and rarely cause tachycardia. They can, however, reduce blood pressure rapidly after the first dose and should be introduced with caution.

Alpha-blockers can be used with other antihypertensive drugs in the treatment of resistant hypertension.

DOXAZOSIN

Cautions care with initial dose (postural hypotension); pulmonary oedema due to aortic or mitral stenosis; cataract surgery (risk of intra-operative floppy iris syndrome); heart failure; **interactions:** Appendix 1 (alpha-blockers)

Driving May affect performance of skilled tasks e.g. driving

Contra-indications history of postural hypotension

Hepatic impairment use with caution; manufacturer advises avoid in severe impairment—no information available

Pregnancy no evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk

Breast-feeding accumulates in milk in *animal* studies—manufacturer advises avoid

Side-effects gastro-intestinal disturbances; oedema, hypotension, postural hypotension, palpitation, tachycardia; dyspnoea, rhinitis, coughing; asthenia, fatigue, vertigo, dizziness, headache, paraesthesia, sleep disturbance, anxiety, depression; influenza-like symptoms; back pain, myalgia; *less commonly* weight changes; angina, myocardial infarction; hypoaesthesia, syncope, tremor, agitation, micturition disturbances, impotence, epistaxis, arthralgia, gout, tinnitus, hypersensitivity reactions (including pruritus, purpura, rash); *very rarely* cholestasis, hepatitis, jaundice, bradycardia, arrhythmias, bronchospasm, hot flushes, gynaecomastia, priapism, abnormal ejaculation, leucopenia, thrombocytopenia, blurred vision, and alopecia

Licensed use not licensed for use in children

Indications and dose

Hypertension (see notes above)

• By mouth

Child 6–12 years 500 micrograms once daily, increased at 1-week intervals to 2–4 mg daily

Child 12–18 years 1 mg daily, increased after 1–2 weeks to 2 mg once daily, and thereafter to 4 mg once daily if necessary; usual max. 4 mg daily (rarely up to 16 mg daily may be required)

Dysfunctional voiding section 7.4.1

Doxazosin (Non-proprietary) (PoM)

Tablets, doxazosin (as mesilate) 1 mg, net price 28-tab pack = 84p; 2 mg, 28-tab pack = 86p; 4 mg, 28-tab pack = £1.03. Counselling, initial dose, driving

Brands include *Doxadura®*

Cardura® (Pfizer) (PoM)

Tablets, doxazosin (as mesilate) 1 mg, net price 28-tab pack = £10.56; 2 mg, 28-tab pack = £14.08.

Counselling, initial dose, driving

Modified-release

Note Children stabilised on immediate-release doxazosin can be transferred to the equivalent dose of modified-release doxazosin

Doxazosin (Non-proprietary) (PoM)

Tablets, m/r, doxazosin (as mesilate) 4 mg, net price 28-tab pack = £5.00. Label: 25, counselling, initial dose, driving

Brands include *Doxadura® XL*, *Dozogen® XL*, *Raporsin® XL*, *Slocinx® XL*

Cardura® XL (Pfizer) (PoM)

Tablets, m/r, doxazosin (as mesilate) 4 mg, net price 28-tab pack = £5.00; 8 mg, 28-tab pack = £9.98.

Label: 25, counselling, initial dose, driving

PAZOSIN

Cautions first dose may cause collapse due to hypotension (therefore should be taken on retiring to bed); cataract surgery (risk of intra-operative floppy iris syndrome); **interactions:** Appendix 1 (alpha-blockers)

Driving May affect performance of skilled tasks e.g. driving

Contra-indications not recommended for congestive heart failure due to mechanical obstruction (e.g. aortic stenosis)

Hepatic impairment start with low doses and adjust according to response

Renal impairment start with low doses in moderate to severe impairment; increase with caution

Pregnancy no evidence of teratogenicity; manufacturer advises use only when potential benefit outweighs risk

Breast-feeding present in milk; manufacturer advises use with caution

Side-effects gastro-intestinal disturbances; postural hypotension, oedema, palpitation; dyspnoea, nasal congestion; drowsiness, headache, depression, nervousness, vertigo; urinary frequency; weakness; blurred vision; *less commonly* tachycardia, insomnia, paraesthesia, sweating, impotence, arthralgia, eye disorders, tinnitus, epistaxis, allergic reactions including rash, pruritus, and urticaria; *rarely* pancreatitis, flushing, vasculitis, bradycardia, hallucinations, worsening of narcolepsy, gynaeomastia, priapism, urinary incontinence, and alopecia

Licensed use not licensed for use in children under 12 years

Indications and dose

Hypertension (see notes above)

• By mouth

Child 1 month–12 years 10–15 micrograms/kg 2–4 times daily (initial dose at bedtime) increased gradually to max. 500 micrograms/kg daily in divided doses (not exceeding 20 mg daily)

Child 12–18 years 500 micrograms 2–3 times daily (initial dose at bedtime), increased after 3–7 days to 1 mg 2–3 times daily for a further 3–7 days; further increased gradually if necessary to max. 20 mg daily in divided doses

Congestive heart failure (but rarely used, see section 2.2)

• By mouth

Child 1 month–12 years 5 micrograms/kg twice daily (initial dose at bedtime), increased gradually to max. 100 micrograms/kg daily in divided doses

Child 12–18 years 500 micrograms 2–4 times daily (initial dose at bedtime), increasing to 4 mg daily in divided doses; maintenance 4–20 mg daily in divided doses

Administration for administration *by mouth*, tablets may be dispersed in water

Prazosin (Non-proprietary) (PoM)

Tablets, prazosin (as hydrochloride) 500 micrograms, net price 56-tab pack = £2.51; 1 mg, 56-tab pack = £3.23; 2 mg, 56-tab pack = £4.39; 5 mg, 56-tab pack = £8.75. Counselling, initial dose, driving

Hypovase® (Pfizer) (PoM)

Tablets, prazosin (as hydrochloride) 500 micrograms, net price 60-tab pack = £2.69; 1 mg, scored, 60-tab pack = £3.46. Counselling, initial dose, driving

Phaeochromocytoma

Long-term management of phaeochromocytoma involves surgery. However, surgery should not take place until there is adequate blockade of both alpha and beta-adrenoceptors. Alpha-blockers are used in the short-term management of hypertensive episodes in phaeochromocytoma. Once alpha blockade is established, tachycardia can be controlled by the cautious addition of a beta-blocker (section 2.4); a cardioselective beta-blocker is preferred. There is no nationwide consensus on the optimal drug regimen or doses used for the management of phaeochromocytoma.

Phenoxybenzamine, a powerful alpha-blocker, is effective in the management of phaeochromocytoma but it has many side-effects.

PHENOXYBENZAMINE HYDROCHLORIDE

Cautions congestive heart failure; severe ischaemic heart disease (see also Contra-indications); cerebrovascular disease (avoid if history of cerebrovascular accident); monitor blood pressure regularly during infusion; carcinogenic in *animals*; avoid in acute porphyria (section 9.8.2); avoid extravasation (irritant to tissues); avoid contact with skin (risk of contact sensitisation)

Contra-indications history of cerebrovascular accident; avoid infusion in hypovolaemia

Renal impairment use with caution

Pregnancy hypotension in newborn may occur

Breast-feeding may be present in milk

Side-effects postural hypotension with dizziness and marked compensatory tachycardia, lassitude, nasal congestion, miosis, inhibition of ejaculation; *rarely* gastro-intestinal disturbances; decreased sweating and dry mouth after intravenous infusion; idiosyncratic profound hypotension within few minutes of starting infusion; convulsions following rapid intravenous infusion also reported

Licensed use not licensed for use in children

Indications and dose

Hypertension in phaeochromocytoma

• By mouth

Child 1 month–18 years 0.5–1 mg/kg twice daily adjusted according to response

• By intravenous infusion

Child 1 month–18 years 0.5–1 mg/kg daily adjusted according to response; occasionally up to 2 mg/kg daily may be required; do not repeat dose within 24 hours

Administration for administration *by mouth*, capsules may be opened.

For *intravenous infusion*, dilute with Sodium Chloride 0.9% and give over at least 2 hours; max. 4 hours between dilution and completion of infusion

Phenoxybenzamine (Non-proprietary) (PoM)

Capsules, phenoxybenzamine hydrochloride 10 mg, net price 30-cap pack = £32.87

Injection concentrate, phenoxybenzamine hydrochloride 50 mg/mL. To be diluted before use. Net price 2-mL amp = £57.14 (hosp. only)

2.5.5 Drugs affecting the renin-angiotensin system

2.5.5.1 Angiotensin-converting enzyme inhibitors

2.5.5.2 Angiotensin-II receptor antagonists

2.5.5.1 Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit the conversion of angiotensin I to angiotensin II. The main indications of ACE inhibitors in

children are shown below. In infants and young children, captopril is often considered first.

Initiation under specialist supervision Treatment with ACE inhibitors should be initiated under specialist supervision and with careful clinical monitoring in children.

Heart failure ACE inhibitors have a valuable role in all grades of heart failure, usually combined with a loop diuretic (section 2.2). Potassium supplements and potassium-sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia. In adults, a low dose of spironolactone may be beneficial in severe heart failure and can be used with an ACE inhibitor provided serum potassium is monitored carefully. Profound first-dose hypotension can occur when ACE inhibitors are introduced to children with heart failure who are already taking a high dose of a loop diuretic (see Cautions below). Temporary withdrawal of the loop diuretic reduces the risk, but can cause severe rebound pulmonary oedema.

Hypertension ACE inhibitors may be considered for hypertension when thiazides and beta-blockers are contra-indicated, not tolerated, or fail to control blood pressure; they may be considered for hypertension in children with type 1 diabetes with nephropathy (see also section 6.1.5). ACE inhibitors can reduce blood pressure very rapidly in some patients particularly in those receiving diuretic therapy (see Cautions, below); the first dose should preferably be given at bedtime.

Diabetic nephropathy For comment on the role of ACE inhibitors in the management of diabetic nephropathy, see section 6.1.5.

Renal effects Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if features mentioned below are present). Hyperkalaemia and other side-effects of ACE inhibitors are more common in children with impaired renal function and the dose may need to be reduced (see Renal Impairment, below).

Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics (or potassium-containing salt substitutes) increase the risk of hyperkalaemia.

In children with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney), ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure. They are therefore contra-indicated in children known to have these forms of critical renovascular disease.

ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in children with severe unilateral renal artery stenosis and a normal contralateral kidney, but glomerular filtration is likely to be reduced (or even abolished) in the affected kidney and the long-term consequences are unknown.

ACE inhibitors are therefore best avoided in those with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If they are used in these circumstances renal function needs to be monitored.

ACE inhibitors should also be used with particular caution in children who may have undiagnosed and clinically silent renovascular disease. ACE inhibitors

are useful for the management of hypertension and proteinuria in children with nephritis. They are thought to have a beneficial effect by reducing intra-glomerular hypertension and protecting the glomerular capillaries and membrane.

Cautions ACE inhibitors need to be initiated with care in children receiving diuretics (**important:** see Concomitant Diuretics, below); first doses can cause hypotension especially in children taking high doses of diuretics, on a low-sodium diet, on dialysis, dehydrated, or with heart failure (see above). Discontinue if marked elevation of hepatic enzymes or jaundice (risk of hepatic necrosis). Renal function should be monitored before and during treatment. For use in pre-existing renovascular disease, see Renal Effects above. The risk of agranulocytosis is possibly increased in collagen vascular disease (blood counts recommended). ACE inhibitors should be used with care in children with severe or symptomatic aortic stenosis (risk of hypotension) and in hypertrophic cardiomyopathy. They should be used with care (or avoided) in those with a history of idiopathic or hereditary angioedema. Children with primary aldosteronism and Afro-Caribbean children may respond less well to ACE inhibitors. **Interactions:** Appendix 1 (ACE inhibitors).

Anaphylactoid reactions To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; they should also be withheld before desensitisation with wasp or bee venom.

Concomitant diuretics ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted children; treatment should therefore be initiated with very low doses. In some children the diuretic dose may need to be reduced or the diuretic discontinued at least 24 hours beforehand (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic therapy cannot be stopped, close observation is recommended after administration of the first dose of ACE inhibitor, for at least 2 hours or until the blood pressure has stabilised.

Contra-indications ACE inhibitors are contra-indicated in children with hypersensitivity to ACE inhibitors (including angioedema) and in bilateral renovascular disease (see also above).

Renal impairment See Renal Effects above; start with low dose and adjust according to response.

Pregnancy ACE inhibitors should be avoided in pregnancy unless essential—they may adversely affect fetal and neonatal blood pressure control and renal function; skull defects and oligohydramnios have also been reported.

Side-effects ACE inhibitors can cause profound hypotension (see Cautions), renal impairment (see Renal Effects above), and a persistent dry cough. They can also cause angioedema (onset may be delayed; higher incidence reported in Afro-Caribbean patients), rash (which may be associated with pruritus and urticaria), pancreatitis, and upper respiratory-tract symptoms such as sinusitis, rhinitis, and sore throat. Gastro-intestinal effects reported with ACE inhibitors include nausea, vomiting, dyspepsia, diarrhoea, constipation, and abdominal pain. Altered liver function tests, cholestatic jaundice, hepatitis, fulminant hepatic necrosis, and hepatic failure have been reported—discontinue if

marked elevation of hepatic enzymes or jaundice. Hyperkalaemia, hypoglycaemia and blood disorders including thrombocytopenia, leucopenia, neutropenia, and haemolytic anaemia have also been reported. Other reported side-effects include headache, dizziness, fatigue, malaise, taste disturbance, paraesthesia, bronchospasm, fever, serositis, vasculitis, myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leucocytosis, and photosensitivity.

Neonates The neonatal response to treatment with ACE inhibitors is very variable, and some neonates develop profound hypotension with even small doses; a test-dose should be used initially and increased cautiously. Adverse effects such as apnoea, seizures, renal failure, and severe unpredictable hypotension are very common in the first month of life and it is therefore recommended that ACE inhibitors are avoided whenever possible, particularly in preterm neonates.

CAPTOPRIL

Cautions see notes above

Contra-indications see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding avoid in first few weeks after delivery, particularly in preterm infants—risk of profound neonatal hypotension; can be used in older infant if essential but monitor infant's blood pressure

Side-effects see notes above; also dry mouth, dyspnoea, sleep disorder, alopecia; *less commonly* tachycardia, palpitation, arrhythmia, angina, pallor, flushing, Raynaud's syndrome; *rarely* stomatitis, anorexia; *very rarely* glossitis, peptic ulcer, syncope, cardiac arrest, cerebrovascular events, cardiogenic shock, allergic alveolitis, eosinophilic pneumonia, confusion, depression, impotence, gynaecomastia, hyponatraemia, blurred vision, photosensitivity, Stevens-Johnson syndrome

Licensed use not licensed for use in children under 18 years

Indications and dose

Hypertension, heart failure, proteinuria in nephritis (under specialist supervision)

• By mouth

Neonate (caution, see neonatal information above) test dose, 10–50 micrograms/kg (10 micrograms/kg in neonate less than 37 weeks corrected gestational age), monitor blood pressure carefully for 1–2 hours; if tolerated give 10–50 micrograms/kg 2–3 times daily increased as necessary to max. 2 mg/kg daily in divided doses (max. 300 micrograms/kg daily in divided doses in neonate less than 37 weeks corrected gestational age)

Child 1 month–12 years test dose, 100 micrograms/kg (max. 6.25 mg), monitor blood pressure carefully for 1–2 hours; if tolerated give 100–300 micrograms/kg 2–3 times a day, increased as necessary to max. 6 mg/kg daily in divided doses (max. 4 mg/kg daily in divided doses for child 1 month–1 year)

Child 12–18 years test dose, 100 micrograms/kg or 6.25 mg, monitor blood pressure carefully for 1–2 hours; if tolerated give 12.5–25 mg 2–3 times a day, increased as necessary to max. 150 mg daily in divided doses

Diabetic nephropathy (under specialist supervision)

• By mouth

Child 12–18 years test dose, 100 micrograms/kg or 6.25 mg, monitor blood pressure carefully for 1–2 hours; if tolerated, give 12.5–25 mg 2–3 times a day, increased as necessary to max. 100 mg daily in divided doses

Administration Administer under close supervision, see notes above. Give test dose whilst child supine. Tablets can be dispersed in water

Captopril (Non-proprietary) (PoM)

Tablets, captopril 12.5 mg, net price 56-tab pack = £2.44; 25 mg, 56-tab pack = £1.28; 50 mg, 56-tab pack = £2.47

Brands include *Ecopace*®, *Kaplon*®

Liquid, various strengths available from 'special-order' manufacturers or specialist importing companies, see p. 840

Capoten® (Squibb) (PoM)

Tablets, scored, captopril 25 mg, net price 28-tab pack = £5.26

Noyada® (Martindale) (PoM)

Oral solution, captopril 5 mg/5 mL, net price 100 mL = £98.21; 25 mg/5 mL, 100 mL = £108.94

Electrolytes Na⁺ approx. 77 micromol/5 mL

ENALAPRIL MALEATE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment monitor closely

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding avoid in first few weeks after delivery, particularly in preterm infants—risk of profound neonatal hypotension; can be used in older infant if essential but monitor infant's blood pressure

Side-effects see notes above; also dyspnoea; depression, asthenia; blurred vision; *less commonly* dry mouth, peptic ulcer, anorexia, ileus; arrhythmias, palpitation, flushing; confusion, nervousness, drowsiness, insomnia, vertigo; impotence; muscle cramps; tinnitus; alopecia, sweating; hyponatraemia; *rarely* stomatitis, glossitis, Raynaud's syndrome, pulmonary infiltrates, allergic alveolitis, abnormal dreams, gynaecomastia, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus; *very rarely* gastro-intestinal angioedema

Licensed use not licensed for use in children for congestive heart failure, proteinuria in nephritis or diabetic nephropathy; not licensed for use in children less than 20 kg for hypertension

Indications and dose

Hypertension, congestive heart failure, proteinuria in nephritis (under specialist supervision)

• By mouth

Neonate (limited information) initially 10 micrograms/kg once daily, monitor blood pressure carefully for 1–2 hours, increased as necessary up to 500 micrograms/kg daily in 1–3 divided doses

Child 1 month–12 years initially 100 micrograms/kg once daily, monitor blood pressure carefully for 1–2 hours, increased as necessary up to max. 1 mg/kg daily in 1–2 divided doses

Child 12–18 years initially 2.5 mg once daily, monitor blood pressure carefully for 1–2 hours, usual maintenance dose 10–20 mg daily in 1–2 divided doses; max. 40 mg daily in 1–2 divided doses if body-weight over 50 kg

Diabetic nephropathy (under specialist supervision)

• By mouth

Child 12–18 years initially 2.5 mg once daily, monitor blood pressure carefully for 1–2 hours, usual maintenance dose 10–20 mg daily in 1–2 divided doses; max. 40 mg daily in 1–2 divided doses if body-weight over 50 kg

Administration tablets may be crushed and suspended in water immediately before use

Enalapril Maleate (Non-proprietary) ^(PoM)

Tablets, enalapril maleate 2.5 mg, net price 28-tab pack = £1.02; 5 mg, 28-tab pack = 90p; 10 mg, 28-tab pack = 97p; 20 mg, 28-tab pack = £1.04

Brands include Ednyl[®]

Liquid, various strengths available from 'special-order' manufacturers or specialist importing companies, see p. 840

Innovace[®] (MSD) ^(PoM)

Tablets, enalapril maleate 2.5 mg, net price 28-tab pack = £5.35; 5 mg (scored), 28-tab pack = £7.51; 10 mg (red), 28-tab pack = £10.53; 20 mg (peach), 28-tab pack = £12.51

LISINAPRIL

Cautions see notes above

Contra-indications see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding avoid—no information available

Side-effects see notes above; also *less commonly* tachycardia, palpitation, cerebrovascular accident, Raynaud's syndrome, confusion, mood changes, vertigo, sleep disturbances, asthenia, impotence; *rarely* dry mouth, gynaecomastia, alopecia, psoriasis; *very rarely* allergic alveolitis, pulmonary infiltrates, profuse sweating, pemphigus, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Licensed use not licensed for use in children

Indications and dose

Hypertension, proteinuria in nephritis (under specialist supervision)

• By mouth

Child 6–12 years initially 70 micrograms/kg (max. 5 mg) once daily, increased in intervals of 1–2 weeks to max. 600 micrograms/kg (or 40 mg) once daily

Child 12–18 years initially 5 mg once daily; usual maintenance dose 10–20 mg once daily; max. 80 mg once daily

Diabetic nephropathy (under specialist supervision)

• By mouth

Child 12–18 years initially 5 mg once daily; usual maintenance dose 10–20 mg once daily; max. 80 mg once daily

Heart failure (adjunct) (under specialist supervision)

• By mouth

Child 12–18 years initially 2.5 mg once daily; increased in steps no greater than 10 mg at intervals of at least 2 weeks up to max. 35 mg once daily if tolerated

Lisinopril (Non-proprietary) ^(PoM)

Tablets, lisinopril (as dihydrate) 2.5 mg, net price 28-tab pack = 94p; 5 mg, 28-tab pack = £1.03; 10 mg, 28-tab pack = 98p; 20 mg, 28-tab pack = £1.04

Liquid, various strengths available from 'special-order' manufacturers or specialist importing companies, see p. 840

Zestril[®] (AstraZeneca) ^(PoM)

Tablets, lisinopril (as dihydrate) 5 mg (pink), net price 28-tab pack = £4.71; 10 mg (pink), 28-tab pack = £7.38; 20 mg (pink), 28-tab pack = £6.51

2.5.5.2 Angiotensin-II receptor antagonists

Candesartan, losartan, and valsartan are specific angiotensin-II receptor antagonists with many properties similar to those of the ACE inhibitors. However, unlike ACE inhibitors, they do not inhibit the breakdown of bradykinin and other kinins, and thus are less likely to cause the persistent dry cough which can complicate ACE inhibitor therapy. They are therefore a useful alternative for children who have to discontinue an ACE inhibitor because of persistent cough.

Candesartan, losartan or valsartan can be used as an alternative to an ACE inhibitor in the management of hypertension.

Cautions Angiotensin-II receptor antagonists should be used with caution in renal artery stenosis (see also Renal Effects under ACE Inhibitors, section 2.5.5.1). Monitoring of plasma-potassium concentration is advised, particularly in children with renal impairment. Angiotensin-II receptor antagonists should be used with caution in aortic or mitral valve stenosis and in hypertrophic cardiomyopathy. They should be used with caution in those with a history of angioedema. Children with primary aldosteronism, and Afro-Caribbean children (particularly those with left ventricular hypertrophy), may not benefit from an angiotensin-II receptor antagonist. **Interactions:** Appendix 1 (angiotensin-II receptor antagonists).

Pregnancy Angiotensin-II receptor antagonists should be avoided in pregnancy, unless essential. They may adversely affect fetal and neonatal blood pressure and renal function; oligohydramnios and neonatal skull defects have also been reported.

Breast-feeding Information on the use of angiotensin-II receptor antagonists in breast-feeding patients is limited, so they are not recommended in these patients. Alternative treatment options, with more established safety information during breast-feeding, are available.

Side-effects Side-effects of angiotensin-II receptor antagonists include symptomatic hypotension (including dizziness), particularly in children with hyponatraemia or intravascular volume depletion (e.g. those taking high-dose diuretics). Hyperkalaemia occurs occa-

sionally; angioedema has also been reported (sometimes with delayed onset).

CANDESARTAN CILEXETIL

Cautions see notes above

Contra-indications cholestasis

Hepatic impairment reduce initial dose in mild or moderate impairment; avoid in severe impairment

Renal impairment see notes above; also reduce initial dose; use with caution if estimated glomerular filtration rate less than 30 mL/minute/1.73m²—no information available

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also cough, vertigo, headache, rash; *less commonly* hyponatraemia; *very rarely* nausea, hepatitis, blood disorders, back pain, arthralgia, myalgia, urticaria, pruritus

Indications and dose

Hypertension (under specialist supervision)

- By mouth

Child 6–18 years

Body-weight less than 50 kg initially 4 mg once daily (lower dose in intravascular volume depletion), adjusted according to response; max. 8 mg once daily

Body-weight 50 kg and over initially 4 mg once daily (lower dose in intravascular volume depletion), adjusted according to response; max. 16 mg once daily

Candesartan Cilexetil (Non-proprietary) (PoM)

Tablets, candesartan cilexetil 2 mg, net price 7-tab pack = £2.11; 4 mg, 7-tab pack = £0.84, 28-tab pack = £1.08; 8 mg, 28-tab pack = £1.62; 16 mg, 28-tab pack = £1.97; 32 mg, 28-tab pack = £3.01

Amias® (Takeda) (PoM)

Tablets, candesartan cilexetil 2 mg (white), net price 7-tab pack = £3.58; 4 mg (white, scored), 7-tab pack = £3.88, 28-tab pack = £9.78; 8 mg (pink, scored), 28-tab pack = £9.89; 16 mg (pink, scored), 28-tab pack = £12.72; 32 mg (pink, scored), 28-tab pack = £16.13

LOSARTAN POTASSIUM

Cautions see notes above; also severe heart failure

Hepatic impairment avoid—no information available

Renal impairment see notes above; also avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73m²—no information available

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also malaise, anaemia; *less commonly* abdominal pain, constipation, diarrhoea, nausea, vomiting, angina, palpitation, oedema, dyspnoea, cough, headache, sleep disorders, drowsiness, urticaria, pruritus, rash; *rarely* hepatitis, atrial fibrillation, cerebrovascular accident, and paraesthesia; *also reported* pancreatitis, depression, erectile dysfunction, thrombocytopenia, hyponatraemia, arthralgia, myalgia, rhabdomyolysis, tinnitus, photosensitivity, and vasculitis (including Henoch-Schönlein purpura)

Indications and dose

Hypertension (under specialist supervision)

- By mouth

Child 6–18 years

Body-weight 20–50 kg initially 700 micrograms/kg (max. 25 mg) once daily (lower dose in intravascular volume depletion), adjusted according to response; max. 50 mg once daily

Body-weight 50 kg and over initially 50 mg once daily (initially 25 mg once daily in intravascular volume depletion), adjusted according to response; max. 1.4 mg/kg (max. 100 mg) once daily

Losartan Potassium (Non-proprietary) (PoM)

Tablets, losartan potassium 12.5 mg, net price 28-tab pack = £5.15; 25 mg, 28-tab pack = £1.11; 50 mg, 28-tab pack = £1.12; 100 mg, 28-tab pack = £1.27

Cozaar® (MSD) (PoM)

Tablets, f/c, losartan potassium 12.5 mg (blue), net price 28-tab pack = £8.09; 25 mg (white), 28-tab pack = £16.18; 50 mg (white, scored), 28-tab pack = £12.80; 100 mg (white), 28-tab pack = £16.18

Oral suspension, losartan potassium 12.5 mg/5 mL when reconstituted with solvent provided, net price 200 mL (berry-citrus flavour) = £53.68

VALSARTAN

Cautions see notes above

Contra-indications biliary cirrhosis, cholestasis

Hepatic impairment max. 80 mg daily in mild to moderate impairment; avoid in severe impairment

Renal impairment see notes above; also avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73m²—no information available

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also *less commonly* abdominal pain, nausea, diarrhoea, cough, malaise, headache; *also reported* anaemia, renal failure, neutropenia, thrombocytopenia, myalgia, vasculitis, serum sickness, rash, pruritus

Licensed use capsules not licensed for use in children

Indications and dose

Hypertension (under specialist supervision)

- By mouth

Child 6–18 years

Body-weight 18–35 kg initially 40 mg once daily, adjusted according to response; max. 80 mg daily

Body-weight 35–80 kg initially 80 mg once daily, adjusted according to response; max. 160 mg daily

Body-weight 80 kg and over initially 80 mg once daily, adjusted according to response; max. 320 mg daily

Valsartan (Non-proprietary) ▼ (PoM)

Tablets, valsartan 40 mg, net price 7-tab pack = £1.97; 80 mg, 28-tab pack = £13.97; 160 mg, 28-tab pack = £18.41; 320 mg, 28-tab pack = £9.06

Diovan® (Novartis) ▼ (PoM)

Capsules, valsartan 40 mg (grey), net price 28-cap pack = £13.97; 80 mg (grey/pink), 28-cap pack = £13.97; 160 mg (grey/pink), 28-cap pack = £18.41
Tablets, f/c, scored, valsartan 40 mg (yellow), net price 7-tab pack = £3.49; 320 mg (dark grey-violet), 28-tab pack = £20.23

2.6 Nitrates, calcium-channel blockers, and other antianginal drugs

2.6.1 Nitrates

2.6.2 Calcium-channel blockers

2.6.3 Other antianginal drugs

2.6.4 Peripheral vasodilators and related drugs

Nitrates and calcium-channel blockers have a vasodilating and, consequently, blood-pressure lowering effect. Vasodilators can act in heart failure by arteriolar dilatation, which reduces both peripheral vascular resistance and left ventricular pressure during systole resulting in improved cardiac output. They can also cause venous dilatation, which results in dilatation of capacitance vessels, increase of venous pooling, and diminution of venous return to the heart (decreasing left ventricular end-diastolic pressure).

2.6.1 Nitrates

Nitrates are potent coronary vasodilators, but their principal benefit follows from a reduction in venous return which reduces left ventricular work. Unwanted effects such as flushing, headache, and postural hypotension may limit therapy, especially if the child is unusually sensitive to the effects of nitrates or is hypovolaemic.

For the use of glyceryl trinitrate in extravasation, see section 10.3.

Children receiving nitrates continuously throughout the day can develop tolerance (with reduced therapeutic effects). Reduction of blood-nitrate concentrations to low levels for 4 to 8 hours each day usually maintains effectiveness in such patients.

GLYCERYL TRINITRATE

Cautions hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction; heart failure due to obstruction; hypoxaemia or other ventilation and perfusion abnormalities; susceptibility to angle-closure glaucoma; metal-containing transdermal systems should be removed before magnetic resonance imaging procedures, cardioversion, or diathermy; avoid abrupt withdrawal; monitor blood pressure and heart rate during infusion; tolerance (see notes above); **interactions:** Appendix 1 (nitrates)

Contra-indications hypersensitivity to nitrates; hypotensive conditions and hypovolaemia; hypertrophic cardiomyopathy; aortic stenosis; cardiac tamponade; constrictive pericarditis; mitral stenosis; toxic pulmonary oedema; raised intracranial pressure

due to cerebral haemorrhage or head trauma; marked anaemia

Hepatic impairment caution in severe impairment

Renal impairment manufacturers advise use with caution in severe impairment

Pregnancy not known to be harmful

Breast-feeding no information available—manufacturers advise use only if potential benefit outweighs risk

Side-effects postural hypotension, tachycardia (but paradoxical bradycardia also reported); throbbing headache, dizziness; *less commonly* nausea, vomiting, heartburn, flushing, syncope, temporary hypoxaemia, rash, application-site reactions with transdermal patches; *very rarely* angle-closure glaucoma

Injection Specific side-effects following injection (particularly if given too rapidly) include severe hypotension, diaphoresis, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitation, abdominal pain; prolonged administration has been associated with methaemoglobinaemia

Licensed use not licensed for use in children

Indications and dose

Hypertension during and after cardiac surgery, heart failure after cardiac surgery, coronary vasoconstriction in myocardial ischaemia, vasoconstriction in shock

• By continuous intravenous infusion

Neonate 0.2–0.5 micrograms/kg/minute, dose adjusted according to response; usual dose 1–3 micrograms/kg/minute; max. 10 micrograms/kg/minute

Child 1 month–18 years initially 0.2–0.5 micrograms/kg/minute, dose adjusted according to response, usual dose 1–3 micrograms/kg/minute; max. 10 micrograms/kg/minute (do not exceed 200 micrograms/minute)

Administration for *continuous intravenous infusion*, dilute to max. concentration of 400 micrograms/mL (but concentration of 1 mg/mL has been used via a central venous catheter) with Glucose 5% or Sodium Chloride 0.9%.

Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used.

Neonatal intensive care, dilute 3 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 1 mL/hour provides a dose of 1 microgram/kg/minute

Glyceryl Trinitrate (Non-proprietary) (PoM)

Injection, glyceryl trinitrate 1 mg/mL, net price 50-mL vial = £15.90

Note To be diluted before use or given undiluted with syringe pump

Injection, glyceryl trinitrate 5 mg/mL, net price 5-mL amp = £6.49; 10-mL amp = £12.98

Excipients may include ethanol, propylene glycol

Note To be diluted before use

Nitrocin® (UCB Pharma) (PoM)

Injection, glyceryl trinitrate 1 mg/mL, net price 10-mL amp = £5.88

Excipients include propylene glycol

Note To be diluted before use or given undiluted with syringe pump

Nitronal® (Merck Serono) (PoM)

Injection, glyceryl trinitrate 1 mg/mL, net price 5-mL vial = £1.80; 50-mL vial = £14.76

Note To be diluted before use or given undiluted with syringe pump

2.6.2 Calcium-channel blockers

Calcium-channel blockers (less correctly called 'calcium-antagonists') interfere with the inward displacement of calcium ions through the slow channels of active cell membranes. They influence the myocardial cells, the cells within the specialised conducting system of the heart, and the cells of vascular smooth muscle. Thus, myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed, and coronary or systemic vascular tone may be diminished.

Calcium-channel blockers differ in their predilection for the various possible sites of action and, therefore, their therapeutic effects are disparate, with much greater variation than those of beta-blockers. There are important differences between verapamil, diltiazem, and the dihydropyridine calcium-channel blockers (amlodipine, nicardipine, nifedipine, and nimodipine). Verapamil and diltiazem should usually be **avoided** in heart failure because they may further depress cardiac function and cause clinically significant deterioration.

Verapamil is used for the treatment of hypertension (section 2.5) and arrhythmias (section 2.3.2). However, it is no longer first-line treatment for arrhythmias in children because it has been associated with fatal collapse especially in infants under 1 year; adenosine is now recommended for first-line use.

Verapamil is a highly negatively inotropic calcium channel-blocker and it reduces cardiac output, slows the heart rate, and may impair atrioventricular conduction. It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension at high doses and should **not** be used with beta-blockers (see p. 107). Constipation is the most common side-effect.

Nifedipine relaxes vascular smooth muscle and dilates coronary and peripheral arteries. It has more influence on vessels and less on the myocardium than does verapamil, and unlike verapamil has no anti-arrhythmic activity. It rarely precipitates heart failure because any negative inotropic effect is offset by a reduction in left ventricular work. Short-acting formulations of nifedipine are not recommended for long-term management of hypertension; their use may be associated with large variations in blood pressure and reflex tachycardia. However, they may be used if a modified-release preparation delivering the appropriate dose is not available or if a child is unable to swallow (a liquid preparation may be prepared using capsules). Nifedipine may also be used for the management of angina due to coronary artery disease in Kawasaki disease or progeria and in the management of Raynaud's syndrome.

Nicardipine has similar effects to those of nifedipine and may produce less reduction of myocardial contractility; it is used to treat hypertensive crisis.

Amlodipine also resembles nifedipine and nicardipine in its effects and does not reduce myocardial contractility or produce clinical deterioration in heart failure. It has a longer duration of action and can be given once daily. Nifedipine and amlodipine are used for the treatment of hypertension. Side-effects associated with vasodilatation such as flushing and headache (which become less obtrusive after a few days), and ankle swelling (which may respond only partially to diuretics) are common.

Nimodipine is related to nifedipine but the smooth muscle relaxant effect preferentially acts on cerebral arteries. Its use is confined to prevention and treatment of vascular spasm following aneurysmal subarachnoid haemorrhage.

Diltiazem is a peripheral vasodilator and also has mild depressor effects on the myocardium. It is used in the treatment of Raynaud's syndrome.

Withdrawal There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of myocardial ischaemia.

AMLODIPINE

Cautions interactions: Appendix 1 (calcium-channel blockers)

Contra-indications cardiogenic shock, significant aortic stenosis

Hepatic impairment may need dose reduction—half-life prolonged

Pregnancy no information available—manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension

Breast-feeding manufacturer advises avoid—no information available

Side-effects abdominal pain, nausea; palpitation, flushing, oedema; headache, dizziness, sleep disturbances, fatigue; *less commonly* gastro-intestinal disturbances, dry mouth, taste disturbances, hypotension, syncope, chest pain, dyspnoea, rhinitis, mood changes, asthenia, tremor, paraesthesia, urinary disturbances, impotence, gynaecomastia, weight changes, myalgia, muscle cramps, back pain, arthralgia, visual disturbances, tinnitus, pruritus, rashes (including isolated reports of erythema multiforme), sweating, alopecia, purpura, and skin discolouration; *very rarely* gastritis, pancreatitis, hepatitis, jaundice, cholestasis, gingival hyperplasia, myocardial infarction, arrhythmias, tachycardia, vasculitis, coughing, peripheral neuropathy, hyperglycaemia, thrombocytopenia, angioedema, and urticaria; **overdosage**: see Emergency Treatment of Poisoning, p. 29

Licensed use not licensed for use in children under 6 years

Indications and dose

Hypertension

• By mouth

Child 1 month–12 years initially 100–200 micrograms/kg once daily; if necessary increase at intervals of 1–2 weeks up to 400 micrograms/kg once daily; max. 10 mg once daily

Child 12–18 years initially 5 mg once daily; if necessary increase at intervals of 1–2 weeks to max. 10 mg once daily

Administration tablets may be dispersed in water

Note Tablets from various suppliers may contain different salts (e.g. amlodipine besilate, amlodipine maleate, and amlodipine mesilate) but the strength is expressed in terms of amlodipine (base); tablets containing different salts are considered interchangeable

Amlodipine (Non-proprietary) (PoM)

Tablets, amlodipine (as maleate or as mesilate) 5 mg, net price 28-tab pack = 89p; 10 mg, 28-tab pack = 94p

Brands include Amlostin®

Istin® (Pfizer) (PoM)

Tablets, amlodipine (as besilate) 5 mg, net price 28-tab pack = £11.08; 10 mg, 28-tab pack = £16.55

DILTIAZEM HYDROCHLORIDE

Cautions heart failure or significantly impaired left ventricular function, bradycardia (avoid if severe), first degree AV block, or prolonged PR interval; **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications severe bradycardia, significant aortic stenosis, cardiogenic shock, left ventricular failure with pulmonary congestion, second- or third-degree AV block (unless pacemaker fitted), sick sinus syndrome; acute porphyria (section 9.8.2)

Hepatic impairment reduce dose

Renal impairment start with smaller dose

Pregnancy avoid

Breast-feeding significant amount present in milk—no evidence of harm but avoid unless no safer alternative

Side-effects bradycardia, sino-atrial block, AV block, palpitation, dizziness, hypotension, malaise, asthenia, headache, hot flushes, gastro-intestinal disturbances, oedema (notably of ankles); rarely rashes (including erythema multiforme and exfoliative dermatitis), photosensitivity; hepatitis, gynaecomastia, gum hyperplasia, extrapyramidal symptoms, depression reported; **overdosage:** see Emergency Treatment of Poisoning, p. 29

Licensed use not licensed for use in children

Indications and dose

Raynaud's syndrome

- By mouth

Child 12–18 years 30–60 mg 2–3 times daily

Standard formulations

Note These formulations are licensed as generics and there is no requirement for brand name dispensing. Although their means of formulation has called for the strict designation 'modified-release' their duration of action corresponds to that of tablets requiring administration more frequently

Diltiazem (Non-proprietary) (PoM)

Tablets, m/r (but see note above), diltiazem hydrochloride 60 mg, net price 84-tab pack = £14.42. Label: 25

Tildiem® (Sanofi-Aventis) (PoM)

Tablets, m/r (but see note above), off-white, diltiazem hydrochloride 60 mg, net price 90-tab pack = £7.96. Label: 25

NICARDIPINE HYDROCHLORIDE

Cautions congestive heart failure or significantly impaired left ventricular function; **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications cardiogenic shock; significant aortic stenosis; acute porphyria (section 9.8.2)

Hepatic impairment half-life prolonged in severe impairment—may need dose reduction

Renal impairment start with smaller dose

Pregnancy may inhibit labour; toxicity in *animal* studies; manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension

Breast-feeding manufacturer advises avoid—no information available

Side-effects dizziness, headache, peripheral oedema, flushing, palpitation, nausea; also gastro-intestinal disturbances, drowsiness, insomnia, tinnitus, hypotension, rashes, dyspnoea, paraesthesia, frequency of micturition; thrombocytopenia, depression and impotence reported; **overdosage:** see Emergency Treatment of Poisoning, p. 29

Licensed use not licensed for use in children

Indications and dose

Hypertensive crisis

- By continuous intravenous infusion

Neonate initially 500 nanograms/kg/minute, adjusted according to response; usual maintenance of 1–4 micrograms/kg/minute

Child 1 month–18 years initially 500 nanograms/kg/minute, adjusted according to response; usual maintenance of 1–4 micrograms/kg/minute (max. 250 micrograms/minute)

Administration for *intravenous infusion*, dilute to a concentration of 100 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; to minimise peripheral venous irritation, change site of infusion every 12 hours

Cardene IV® (PoM)

Injection, nicardipine 2.5 mg/mL (10-mL ampoule) Available from 'special-order' manufacturers or specialist importing companies, see p. 840

NIFEDIPINE

Cautions see notes above; also poor cardiac reserve; heart failure or significantly impaired left ventricular function (heart failure deterioration observed); severe hypotension; diabetes mellitus; **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications cardiogenic shock; significant aortic stenosis

Hepatic impairment dose reduction may be required in severe liver disease

Pregnancy may inhibit labour; manufacturer advises avoid before week 20, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension; use only if other treatment options are not indicated or have failed

Breast-feeding amount too small to be harmful but manufacturer advises avoid

Side-effects gastro-intestinal disturbance; hypotension, oedema, vasodilatation, palpitation; headache, dizziness, lethargy, asthenia; *less commonly* tachycardia, hypotension, syncope, chills, nasal congestion, dyspnoea, anxiety, sleep disturbance, vertigo, migraine, paraesthesia, tremor, polyuria, dysuria, nocturia, erectile dysfunction, epistaxis, myalgia, joint swelling, visual disturbance, sweating, and hypersensitivity reactions (including angioedema, jaundice, pruritus, urticaria, and rash); *rarely* anorexia, gum hyperplasia, mood disturbances, hyperglycaemia, male infertility, purpura, and photosensitivity reactions; also reported dysphagia, intestinal obstruction, intestinal ulcer, bezoar formation, gynaecomastia, agranulocytosis, and anaphylaxis; **overdosage:** see Emergency Treatment of Poisoning, p. 29

Licensed use not licensed for use in children

Indications and dose**Hypertensive crisis, acute angina in Kawasaki disease or progeria**

- By mouth (see Administration, below)

Child 1 month–18 years 250–500 micrograms/kg (max. 20 mg) as a single dose

Hypertension, angina in Kawasaki disease or progeria

- By mouth

Child 1 month–12 years 200–300 micrograms/kg 3 times daily; max. 3 mg/kg daily or 90 mg daily

Child 12–18 years 5–20 mg 3 times daily; max. 90 mg daily

Note Dose frequency depends on preparation used

Raynaud's syndrome

- By mouth

Child 2–18 years 2.5–10 mg 2–4 times daily; start with low doses at night and increase gradually to avoid postural hypotension

Note Dose frequency depends on preparation used

Persistent hyperinsulinaemic hypoglycaemia see also section 6.1.4

- By mouth

Neonate 100–200 micrograms/kg (max. 600 micrograms/kg) 4 times daily

Administration for rapid effect in *hypertensive crisis* or *acute angina*, bite capsules and swallow liquid or use liquid preparation if 5-mg or 10-mg dose inappropriate; if liquid unavailable, extract contents of capsule via a syringe and use immediately—cover syringe with foil to protect contents from light; capsule contents may be diluted with water if necessary. Modified-release tablets may be crushed—this may alter the release profile; crushed tablets should be administered within 30–60 seconds to avoid significant loss of potency of drug

Nifedipine (Non-proprietary) (PoM)

Capsules, nifedipine 5 mg, net price 84-cap pack = £10.26; 10 mg, 84-cap pack = £6.95

Dose

Give 3 times daily

Oral liquid, available from 'special-order' manufacturers or specialist importing companies, see p. 840

Adalat® (Bayer) (PoM)

Capsules, orange, nifedipine 5 mg, net price 90-cap pack = £5.73; 10 mg, 90-cap pack = £7.30

Note Adalat liquid gel capsules contain 5 mg nifedipine in 0.17 mL and 10 mg nifedipine in 0.34 mL

Dose

Give 3 times daily

Modified release

Note Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of nifedipine, prescribers should specify the brand to be dispensed. Modified-release formulations may not be suitable for dose titration in hepatic disease

Adalat® LA (Bayer) (PoM)

LA 20 tablets, m/r, f/c, pink, nifedipine 20 mg, net price 28-tab pack = £5.27. Label: 25

LA 30 tablets, m/r, f/c, pink, nifedipine 30 mg, net price 28-tab pack = £6.85. Label: 25

LA 60 tablets, m/r, f/c, pink, nifedipine 60 mg, net price 28-tab pack = £9.03. Label: 25

Counselling Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy

Cautions dose form not appropriate for use in hepatic impairment or where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, or inflammatory bowel disease (including Crohn's disease)

Dose

Give once daily

Adalat® Retard (Bayer) (PoM)

Retard 10 tablets, m/r, f/c, grey-pink, nifedipine 10 mg, net price 56-tab pack = £7.34. Label: 25

Retard 20 tablets, m/r, f/c, grey-pink, nifedipine 20 mg, net price 56-tab pack = £8.81. Label: 25

Dose

Give twice daily

Adipine® MR (Chiesi) (PoM)

Tablets, m/r, nifedipine 10 mg (pink), net price 56-tab pack = £3.73; 20 mg (pink), 56-tab pack = £5.21. Label: 25

Dose

Give twice daily

Adipine® XL (Chiesi) (PoM)

Tablets, m/r, red, nifedipine 30 mg, net price 28-tab pack = £4.70; 60 mg, 28-tab pack = £7.10. Label: 25

Dose

Give once daily

Coracten SR® (UCB Pharma) (PoM)

Capsules, m/r, nifedipine 10 mg (grey/pink, enclosing yellow pellets), net price 60-cap pack = £3.90; 20 mg (pink/brown, enclosing yellow pellets), 60-cap pack = £5.41. Label: 25

Dose

Give twice daily

Coracten XL® (UCB Pharma) (PoM)

Capsules, m/r, nifedipine 30 mg (brown), net price 28-cap pack = £4.89; 60 mg (orange), 28-cap pack = £7.34. Label: 25

Dose

Give once daily

Fortipine LA 40® (AMCo) (PoM)

Tablets, m/r, red, nifedipine 40 mg, net price 30-tab pack = £14.40. Label: 21, 25

Dose

Give 1–2 times daily

Nifedipress® MR (Dexcel) (PoM)

Tablets, m/r, pink, nifedipine 10 mg, net price 56-tab pack = £9.23; 20 mg, 56-tab pack = £10.06. Label: 25

Dose

Give twice daily

Note Also available as *Calchan® MR*

Tensipine MR® (Genus) (PoM)

Tablets, m/r, pink-grey, nifedipine 10 mg, net price 56-tab pack = £4.30; 20 mg, 56-tab pack = £5.49. Label: 25

Dose

Give twice daily

Valni Xl® (Winthrop) (PoM)

Tablets, m/r, red, nifedipine 30 mg, net price 28-tab pack = £7.29; 60 mg, 28-tab pack = £9.14. Label: 25

Cautions dose form not appropriate for use in hepatic impairment, or where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, inflammatory bowel disease, or ileostomy after proctocolectomy

Dose

Give once daily

NIMODIPINE

Cautions cerebral oedema or severely raised intracranial pressure; hypotension; avoid concomitant administration of nimodipine tablets and infusion, other calcium-channel blockers, or beta-blockers; concomitant nephrotoxic drugs; **interactions:** Appendix 1 (calcium-channel blockers, alcohol (infusion only))

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment elimination reduced in cirrhosis—monitor blood pressure

Renal impairment manufacturer advises monitor renal function closely with intravenous administration

Pregnancy manufacturer advises use only if potential benefit outweighs risks

Breast-feeding manufacturer advises avoid—present in milk

Side-effects hypotension, variation in heart-rate, flushing, headache, gastro-intestinal disorders, nausea, sweating and feeling of warmth; thrombocytopenia and ileus reported; **overdosage:** see Emergency Treatment of Poisoning, p. 29

Licensed use not licensed for use in children

Indications and dose

Treatment of vasospasm following subarachnoid haemorrhage under specialist advice only

- By intravenous infusion

Child 1 month–12 years initially 15 micrograms/kg/hour (max. 500 micrograms/hour) or initially 7.5 micrograms/kg/hour if blood pressure unstable; increase after 2 hours to 30 micrograms/kg/hour (max. 2 mg/hour) if no severe decrease in blood pressure; continue for at least 5 days (max. 14 days)

Child 12–18 years initially 500 micrograms/hour (up to 1 mg/hour if body-weight over 70 kg and blood pressure stable), increase after 2 hours to 1–2 mg/hour if no severe fall in blood pressure; continue for at least 5 days (max. 14 days)

Prevention of vasospasm following subarachnoid haemorrhage

- By mouth

Child 1 month–18 years 0.9–1.2 mg/kg (max. 60 mg) 6 times daily, starting within 4 days of haemorrhage and continued for 21 days

Administration for continuous intravenous infusion, administer undiluted via a Y-piece on a central venous catheter connected to a running infusion of Glucose 5%, or Sodium Chloride 0.9%; not to be added to an infusion container; incompatible with polyvinyl chloride giving sets or containers; protect infusion from light.

For administration by mouth, tablets may be crushed or halved but are light sensitive—administer immediately

Nimotop® (Bayer) (PoM)

Tablets, yellow, f/c, nimodipine 30 mg, net price 100-tab pack = £40.00

Intravenous infusion, nimodipine 200 micrograms/mL; also contains ethanol 20% and macrogol '400' 17%. Net price 50-mL vial (with polyethylene infusion catheter) = £13.60

Note Polyethylene, polypropylene, or glass apparatus should be used; PVC should be avoided

VERAPAMIL HYDROCHLORIDE

Cautions first-degree AV block; patients taking beta-blockers (**important:** see below); **interactions:** Appendix 1 (calcium-channel blockers)

Verapamil and beta-blockers Verapamil injection should not be given to patients recently treated with beta-blockers because of the risk of hypotension and asystole. The suggestion that when verapamil injection has been given first, an interval of 30 minutes before giving a beta-blocker is sufficient has not been confirmed.

It may also be hazardous to give verapamil and a beta-blocker together by mouth (should only be contemplated if myocardial function well preserved).

Contra-indications hypotension, bradycardia, second- and third-degree AV block, sick sinus syndrome, cardiogenic shock, sino-atrial block; history of heart failure or significantly impaired left ventricular function, even if controlled by therapy; atrial flutter or fibrillation complicating syndromes associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome); acute porphyria (section 9.8.2)

Hepatic impairment oral dose may need to be reduced

Pregnancy may reduce uterine blood flow with fetal hypoxia; manufacturer advises avoid during first trimester unless absolutely necessary; may inhibit labour

Breast-feeding amount too small to be harmful

Side-effects constipation; *less commonly* nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; *rarely* allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia after long-term treatment; after intravenous administration or high doses, hypotension, heart failure, bradycardia, heart block, and asystole; hypersensitivity reactions involving reversibly raised liver function tests; **overdosage:** see Emergency Treatment of Poisoning, p. 29

Licensed use Modified release preparation not licensed for use in children

Indications and dose

Hypertension, prophylaxis of supraventricular arrhythmias under specialist advice only

- By mouth

Child 1–2 years 20 mg 2–3 times daily

Child 2–18 years 40–120 mg 2–3 times daily

Treatment of supraventricular arrhythmias

- By intravenous injection over 2–3 minutes (with ECG and blood-pressure monitoring and under specialist advice)

Child 1–18 years 100–300 micrograms/kg (max. 5 mg) as a single dose, repeated after 30 minutes if necessary

Administration for *intravenous injection*, may be diluted with Glucose 5% or Sodium Chloride 0.9%; incompatible with solutions of pH greater than 6

Verapamil (Non-proprietary) (PoM)

Tablets, coated, verapamil hydrochloride 40 mg, net price 84-tab pack = £1.51; 80 mg, 84-tab pack = £1.92; 120 mg, 28-tab pack = £1.43; 160 mg, 56-tab pack = £28.20

Oral solution, verapamil hydrochloride 40 mg/5 mL, net price 150 mL = £36.90

Brands include Zolvera®

Cordilox® (Dexcel) (PoM)

Tablets, yellow, f/c, verapamil hydrochloride 40 mg, net price 84-tab pack = £1.50; 80 mg, 84-tab pack = £2.05; 120 mg, 28-tab pack = £1.15; 160 mg, 56-tab pack = £2.80

Injection, verapamil hydrochloride 2.5 mg/mL, net price 2-mL amp = £1.11

Securon® (Abbott Healthcare) (PoM)

Injection, verapamil hydrochloride 2.5 mg/mL, net price 2-mL amp = £1.08

Modified release

Half Securon SR® (Abbott Healthcare) (PoM)

Tablets, m/r, f/c, verapamil hydrochloride 120 mg, net price 28-tab pack = £7.71. Label: 25

Dose

Give once daily (doses above 240 mg daily, give 2–3 times daily)

Securon SR® (Abbott Healthcare) (PoM)

Tablets, m/r, pale green, f/c, scored, verapamil hydrochloride 240 mg, net price 28-tab pack = £5.55. Label: 25

Dose

Give once daily (doses above 240 mg daily, give 2–3 times daily)

Univer® (TEVA UK) (PoM)

Capsules, m/r, verapamil hydrochloride 120 mg (yellow/dark blue), net price 28-cap pack = £4.86; 180 mg (yellow), 56-cap pack = £11.38; 240 mg (yellow/dark blue), 28-cap pack = £7.67. Label: 25

Excipients include propylene glycol (see Excipients, p. 2)

Dose

Give once daily

Verapress MR® (Dexcel) (PoM)

Tablets, m/r, pale green, f/c, verapamil hydrochloride 240 mg, net price 28-tab pack = £9.90. Label: 25

Dose

Give 1–2 times daily

Note Also available as *Cordilox® MR*

Vertab® SR 240 (Chiesi) (PoM)

Tablets, m/r, pale green, f/c, scored, verapamil hydrochloride 240 mg, net price 28-tab pack = £5.45. Label: 25

Dose

Give 1–2 times daily

2.6.4 Peripheral vasodilators and related drugs

Raynaud's syndrome consists of recurrent, long-lasting, and episodic vasospasm of the fingers and toes often associated with exposure to cold. Management includes avoidance of exposure to cold and stopping smoking (if appropriate). More severe symptoms may require vasodilator treatment, which is most often successful in primary Raynaud's syndrome. **Nifedipine** and **diltiazem** (section 2.6.2) are useful for reducing the frequency and severity of vasospastic attacks. In very severe cases, where digital infarction is likely, intravenous infusion of the prostacyclin analogue **iloprost** may be helpful.

Vasodilator therapy is not established as being effective for *chilblains* (section 13.13).

ILOPROST

Cautions see section 2.5.1.2

Contra-indications see section 2.5.1.2

Hepatic impairment dose may need to be halved in liver cirrhosis

Side-effects see section 2.5.1.2

Licensed use not licensed for use in children

Indications and dose

Raynaud's syndrome see notes above

- By intravenous infusion

Child 12–18 years initially 30 nanograms/kg/hour, increased gradually to 60–120 nanograms/kg/hour given over 6 hours daily for 3–5 days

Pulmonary hypertension section 2.5.1.2

Administration for *intravenous infusion*, dilute to a concentration of 200 nanograms/mL with Glucose 5% or Sodium Chloride 0.9%; alternatively, may be diluted to a concentration of 2 micrograms/mL and given via syringe driver

Iloprost (Non-proprietary)

Concentrate for infusion, iloprost (as trometamol) 100 micrograms/mL

For dilution and use as an intravenous infusion

Note available on a named patient basis from Bayer Schering in 0.5 mL and 1 mL ampoules

2.7 Sympathomimetics

2.7.1 Inotropic sympathomimetics

2.7.2 Vasoconstrictor sympathomimetics

2.7.3 Cardiopulmonary resuscitation

The properties of sympathomimetics vary according to whether they act on alpha or on beta adrenergic receptors. Response to sympathomimetics can also vary considerably in children, particularly neonates. It is important to titrate the dose to the desired effect and to monitor the child closely.

2.7.1 Inotropic sympathomimetics

The cardiac stimulants **dobutamine** and **dopamine** act on beta₁ receptors in cardiac muscle and increase contractility with little effect on rate.

2.6.3 Other antianginal drugs

Classification not used in *BNF for Children*.

Dopamine has a variable, unpredictable, and dose dependent impact on vascular tone. Low dose infusion (2 micrograms/kg/minute) normally causes vasodilatation, but there is little evidence that this is clinically beneficial; moderate doses increase myocardial contractility and cardiac output in older children, but in neonates moderate doses may cause a reduction in cardiac output. High doses cause vasoconstriction and increase vascular resistance, and should therefore be used with caution following cardiac surgery, or where there is co-existing neonatal pulmonary hypertension.

In neonates the response to inotropic sympathomimetics varies considerably, particularly in those born prematurely; careful dose titration and monitoring are necessary.

Isoprenaline injection is available from 'special-order' manufacturers or specialist importing companies, see p. 840.

Shock Shock is a medical emergency associated with a high mortality. The underlying causes of shock such as haemorrhage, sepsis or myocardial insufficiency should be corrected. Additional treatment is dependent on the type of shock.

Septic shock is associated with severe hypovolaemia (due to vasodilation and capillary leak) which should be corrected with crystalloids or colloids (section 9.2.2). If hypotension persists despite volume replacement, **dopamine** should be started. For shock refractory to treatment with dopamine, if cardiac output is high and peripheral vascular resistance is low (warm shock), **noradrenaline** (norepinephrine) (section 2.7.2) should be added or if cardiac output is low and peripheral vascular resistance is high (cold shock), **adrenaline** (epinephrine) (section 2.7.2) should be added. Additionally, in cold shock, a vasodilator such as **milrinone** (section 2.1.2), **glyceryl trinitrate** (section 2.6.1), or **sodium nitroprusside** (on specialist advice only) (section 2.5.1.1) can be used to reduce vascular resistance.

If the shock is resistant to volume expansion and catecholamines, and there is suspected or proven adrenal insufficiency, low dose **hydrocortisone** (section 6.3.2) can be used. ACTH-stimulated plasma-cortisol concentration should be measured; however, hydrocortisone can be started without such information.

Alternatively, if the child is resistant to catecholamines, and vascular resistance is low, **vasopressin** (section 6.5.2) can be added.

Neonatal septic shock can be complicated by the transition from fetal to neonatal circulation. Treatment to reverse right ventricular failure, by decreasing pulmonary artery pressures, is commonly needed in neonates with fluid-refractory shock and persistent pulmonary hypertension of the newborn (section 2.5.1.2). Rapid administration of fluid in neonates with patent ductus arteriosus may cause left-to-right shunting and congestive heart failure induced by ventricular overload.

In *cardiogenic shock*, the aim is to improve cardiac output and to reduce the afterload on the heart. If central venous pressure is low, cautious volume expansion with a colloid or crystalloid can be used. An inotrope such as **adrenaline** (epinephrine) (section 2.7.2) or **dopamine** should be given to increase cardiac output. **Dobutamine** is a peripheral vasodilator and is an alternative if hypotension is not significant.

Milrinone (section 2.1.2) has both inotropic and vasodilatory effects and can be used when vascular resistance is high. Alternatively, **glyceryl trinitrate** (2.6.1) or **sodium nitroprusside** (on specialist advice only) (section 2.5.1.1) can be used to reduce vasoconstriction.

Hypovolaemic shock should be treated with a crystalloid or colloid solution (or whole or reconstituted blood if source of hypovolaemia is haemorrhage) and further steps to improve cardiac output and decrease vascular resistance can be taken, as in cardiogenic shock.

The use of sympathomimetic inotropes and vasoconstrictors should preferably be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

For advice on the management of anaphylactic shock, see section 3.4.3.

DOBUTAMINE

Cautions arrhythmias, acute myocardial infarction, acute heart failure, severe hypotension, marked obstruction of cardiac ejection (such as idiopathic hypertrophic subaortic stenosis); correct hypovolaemia before starting treatment; tolerance may develop with continuous infusions longer than 72 hours; hyperthyroidism; **interactions:** Appendix 1 (sympathomimetics)

Contra-indications pheochromocytoma

Pregnancy no evidence of harm in *animal studies*—manufacturers advise use only if benefit outweighs risk

Breast-feeding manufacturers advise avoid—no information available

Side-effects nausea; hypotension, hypertension (marked increase in systolic blood pressure indicates overdose), arrhythmias, palpitation, chest pain; dyspnoea, bronchospasm; headache; fever; increased urinary urgency; eosinophilia; rash, phlebitis; *very rarely* myocardial infarction, hypokalaemia; *also reported* coronary artery spasm and thrombocytopenia

Licensed use strong sterile solution not licensed for use in children

Indications and dose

Inotropic support in low cardiac output states, after cardiac surgery, cardiomyopathies, shock

• By continuous intravenous infusion

Neonate initially 5 micrograms/kg/minute, adjusted according to response to 2–15 micrograms/kg/minute; max. 20 micrograms/kg/minute

Child 1 month–18 years initially 5 micrograms/kg/minute adjusted according to response to 2–20 micrograms/kg/minute

Administration for *continuous intravenous infusion*, using infusion pump, dilute to a concentration of 0.5–1 mg/mL (max. 5 mg/mL if fluid restricted) with Glucose 5% or Sodium Chloride 0.9%; infuse higher concentration solutions through central venous catheter only. Incompatible with bicarbonate and other strong alkaline solutions.

Neonatal intensive care, dilute 30 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.5 mL/hour provides a dose of 5 micrograms/kg/minute

Dobutamine (Non-proprietary) [PoM]

Injection, dobutamine (as hydrochloride) 5 mg/mL, net price 50-mL vial = £7.50

Excipients may include sulfites

Note To be diluted before use or given undiluted with syringe pump

Concentrate for intravenous infusion, dobutamine (as hydrochloride) 12.5 mg/mL, net price 20-mL amp = £5.20

Excipients may include sulfites

Note To be diluted before use

DOPAMINE HYDROCHLORIDE

Cautions correct hypovolaemia; hyperthyroidism; interactions: Appendix 1 (sympathomimetics)

Contra-indications tachyarrhythmia, pheochromocytoma

Pregnancy no evidence of harm in *animal* studies—manufacturer advises use only if potential benefit outweighs risk

Breast-feeding may suppress lactation—not known to be harmful

Side-effects nausea, vomiting, chest pain, palpitation, tachycardia, vasoconstriction, hypotension, dyspnoea, headache; *less commonly* bradycardia, hypertension, gangrene, mydriasis; *rarely* fatal ventricular arrhythmias

Licensed use not licensed for use in children under 12 years

Indications and dose

To correct the haemodynamic imbalance due to acute hypotension, shock, cardiac failure, adjunct following cardiac surgery

- By continuous intravenous infusion

Neonate initially 3 micrograms/kg/minute, adjusted according to response (max. 20 micrograms/kg/minute)

Child 1 month–18 years initially 5 micrograms/kg/minute adjusted according to response (max. 20 micrograms/kg/minute)

Administration for *continuous intravenous infusion*, dilute to a max. concentration of 3.2 mg/mL with Glucose 5% or Sodium Chloride 0.9%. Infuse higher concentrations through central venous catheter using a syringe pump to avoid extravasation and fluid overload. Incompatible with bicarbonate and other alkaline solutions.

Neonatal intensive care, dilute 30 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.3 mL/hour provides a dose of 3 micrograms/kg/minute

Dopamine (Non-proprietary) [PoM]

Concentrate for intravenous infusion, dopamine hydrochloride 40 mg/mL, net price 5-mL amp = £3.88; 160 mg/mL, 5-mL amp = £3.40.

Note To be diluted before use

Intravenous infusion, dopamine hydrochloride 1.6 mg/mL in glucose 5% intravenous infusion Available from 'special-order' manufacturers or specialist importing companies, see p. 840

to constrict peripheral vessels. They are sometimes used as an emergency method of elevating blood pressure where other measures have failed (see also section 2.7.1).

The danger of vasoconstrictors is that although they raise blood pressure they also reduce perfusion of vital organs such as the kidney.

Ephedrine is used to reverse hypotension caused by spinal and epidural anaesthesia.

Metaraminol is used as a vasopressor during cardiopulmonary bypass.

Phenylephrine causes peripheral vasoconstriction and increases arterial pressure.

Ephedrine, metaraminol and phenylephrine are rarely needed in children and should be used under specialist supervision.

Noradrenaline (norepinephrine) is reserved for children with low systemic vascular resistance that is unresponsive to fluid resuscitation following septic shock, spinal shock, and anaphylaxis.

Adrenaline (epinephrine) is mainly used for its inotropic action. Low doses (acting on beta receptors) cause systemic and pulmonary vasodilation, with some increase in heart rate and stroke volume and also an increase in contractility; high doses act predominantly on alpha receptors causing intense systemic vasoconstriction.

EPHEDRINE HYDROCHLORIDE

Cautions hyperthyroidism, diabetes mellitus, hypertension, susceptibility to angle-closure glaucoma, interactions: Appendix 1 (sympathomimetics)

Renal impairment use with caution

Pregnancy increased fetal heart rate reported with parenteral ephedrine

Breast-feeding irritability and disturbed sleep reported

Side-effects nausea, vomiting, anorexia; tachycardia (sometimes bradycardia), arrhythmias, anginal pain, vasoconstriction with hypertension, vasodilation with hypotension, dizziness and flushing; dyspnoea; headache, anxiety, restlessness, confusion, psychoses, insomnia, tremor; difficulty in micturition, urine retention; sweating, hypersalivation; changes in blood-glucose concentration; *very rarely* angle-closure glaucoma

Indications and dose

Reversal of hypotension from epidural and spinal anaesthesia

- By slow intravenous injection of a solution containing ephedrine hydrochloride 3 mg/mL

Child 1–12 years 500–750 micrograms/kg or 17–25 mg/m² every 3–4 minutes according to response; max. 30 mg during episode

Child 12–18 years 3–7.5 mg (max. 9 mg) repeated every 3–4 minutes according to response, max. 30 mg during episode

Nasal congestion section 12.2.2

Administration for *slow intravenous injection*, give via central venous catheter

2.7.2 Vasoconstrictor sympathomimetics

Vasoconstrictor sympathomimetics raise blood pressure transiently by acting on alpha-adrenergic receptors

Ephedrine Hydrochloride (Non-proprietary) (PoM)

Injection, ephedrine hydrochloride 3 mg/mL, net price 10-mL amp = £6.34; 30 mg/mL, net price 1-mL amp = 41p

METARAMINOL

Cautions see under Noradrenaline; longer duration of action than noradrenaline (norepinephrine), see below; cirrhosis; **interactions:** Appendix 1 (sympathomimetics)

Hypertensive response Metaraminol has a longer duration of action than noradrenaline, and an excessive vasopressor response may cause a prolonged rise in blood pressure

Contra-indications see under Noradrenaline

Pregnancy may reduce placental perfusion—manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises caution—no information available

Side-effects see under Noradrenaline; also tachycardia; fatal ventricular arrhythmia reported in Laennec's cirrhosis

Licensed use not licensed for use in children

Indications and dose**Acute hypotension**

- By intravenous infusion

Child 12–18 years 15–100 mg adjusted according to response

Emergency treatment of acute hypotension

- By intravenous administration

Child 12–18 years initially by *intravenous injection* 0.5–5 mg, then by *intravenous infusion* 15–100 mg adjusted according to response

Administration for *intravenous infusion*, dilute to a concentration of 30–200 micrograms/mL with Glucose 5% or Sodium Chloride 0.9% and give through a central venous catheter

Metaraminol (Non-proprietary) (PoM)

Injection, metaraminol 10 mg (as tartrate) mL.

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

NORADRENALINE/NOREPINEPHRINE

Cautions coronary, mesenteric, or peripheral vascular thrombosis; following myocardial infarction; Prinzmetal's variant angina, hyperthyroidism, diabetes mellitus; hypoxia or hypercapnia; uncorrected hypovolaemia; extravasation at injection site may cause necrosis; susceptibility to angle-closure glaucoma; **interactions:** Appendix 1 (sympathomimetics)

Contra-indications hypertension (monitor blood pressure and rate of flow frequently)

Pregnancy avoid—may reduce placental perfusion

Side-effects anorexia, nausea, vomiting, hypoxia, arrhythmias, peripheral ischaemia, palpitation, hypertension, bradycardia, tachycardia, dyspnoea, headache, insomnia, confusion, anxiety, psychosis, weakness, tremor, urinary retention, angle-closure glaucoma

Licensed use not licensed for use in children

Indications and dose

Acute hypotension (septic shock) or shock secondary to excessive vasodilation (as noradrenaline)

- By continuous intravenous infusion

Neonate 20–100 nanograms (base)/kg/minute adjusted according to response; max. 1 microgram (base)/kg/minute

Child 1 month–18 years 20–100 nanograms (base)/kg/minute adjusted according to response; max. 1 microgram (base)/kg/minute

Note 1 mg of noradrenaline base is equivalent to 2 mg of noradrenaline acid tartrate. Dose expressed as the base

Administration for *continuous intravenous infusion*, dilute to a max. concentration of noradrenaline (base) 40 micrograms/mL (higher concentrations can be used if fluid-restricted) with Glucose 5% or Sodium Chloride and Glucose. Infuse through central venous catheter; discard if discoloured. Incompatible with bicarbonate or alkaline solutions.

Neonatal intensive care, dilute 600 micrograms (base)/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 20 nanograms (base)/kg/minute

Noradrenaline/Norepinephrine (Non-proprietary) (PoM)

Injection, noradrenaline base 1 mg/mL (as noradrenaline acid tartrate 2 mg/mL). For dilution before use. Net price 2-mL amp = £2.20, 4-mL amp = £4.40, 20-mL amp = £6.35

Note For a period of time preparations on the UK market may be described as *either* noradrenaline base or noradrenaline acid tartrate; doses above are expressed as the base

PHENYLEPHRINE HYDROCHLORIDE

Cautions see under Noradrenaline; longer duration of action than noradrenaline (norepinephrine), see below; coronary disease

Hypertensive response Phenylephrine has a longer duration of action than noradrenaline, and an excessive vasopressor response may cause a prolonged rise in blood pressure

Contra-indications see under Noradrenaline; severe hyperthyroidism

Pregnancy avoid if possible; malformations reported following use in first trimester; fetal hypoxia and bradycardia reported in late pregnancy and labour

Side-effects see under Noradrenaline; also tachycardia or reflex bradycardia

Licensed use not licensed for use in children by intravenous infusion or injection

Indications and dose**Acute hypotension**

- By subcutaneous or intramuscular injection (but intravenous injection preferred, see below)

Child 1–12 years 100 micrograms/kg every 1–2 hours as needed (max. 5 mg)

Child 12–18 years 2–5 mg, followed if necessary after at least 15 minutes by further doses of 1–10 mg (max. initial dose 5 mg)

- By slow intravenous injection

Child 1–12 years 5–20 micrograms/kg (max. 500 micrograms) repeated as necessary after at least 15 minutes

Child 12–18 years 100–500 micrograms repeated as necessary after at least 15 minutes

• **By intravenous infusion**

Child 1–16 years 100–500 nanograms/kg/minute, adjusted according to response

Child 16–18 years initially up to 180 micrograms/minute reduced to 30–60 micrograms/minute according to response

Administration for *intravenous injection*, dilute to a concentration of 1 mg/mL with Water for Injections and administer slowly.

For *intravenous infusion*, dilute to a concentration of 20 micrograms/mL with Glucose 5% or Sodium Chloride 0.9% and administer as a continuous infusion via a central venous catheter using a controlled infusion device

Phenylephrine (Non-proprietary) (Pom)

Injection, phenylephrine hydrochloride 10 mg/mL (1%), net price 1-mL amp = £9.91

ADRENALINE/EPINEPHRINE

Cautions ischaemic heart disease, severe angina, obstructive cardiomyopathy, hypertension, arrhythmias, cerebrovascular disease; occlusive vascular disease, monitor blood pressure and ECG; cor pulmonale; organic brain damage, psychoneurosis; pheochromocytoma; diabetes mellitus, hyperthyroidism; hypokalaemia, hypercalcaemia; susceptibility to angle-closure glaucoma; **interactions:** Appendix 1 (sympathomimetics)

Renal impairment manufacturers advise use with caution in severe impairment

Pregnancy may reduce placental perfusion and can delay second stage of labour; manufacturers advise use only if benefit outweighs risk

Breast-feeding present in milk but unlikely to be harmful as poor oral bioavailability

Side-effects nausea, vomiting, dry mouth, anorexia, hypersalivation; arrhythmias, palpitation, tachycardia, syncope, angina, hypertension (risk of cerebral haemorrhage), cold extremities, pallor; dyspnoea, pulmonary oedema (on excessive dosage or extreme sensitivity); anxiety, tremor, restlessness, headache, insomnia, confusion, weakness, dizziness, hallucinations, psychosis; hyperglycaemia; difficulty in micturition, urinary retention; metabolic acidosis; hypokalaemia; mydriasis, angle-closure glaucoma; tissue necrosis at injection site and of extremities, liver and kidneys, sweating

Indications and dose

Acute hypotension

• **By continuous intravenous infusion**

Neonate initially 100 nanograms/kg/minute adjusted according to response; higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension

Child 1 month–18 years initially 100 nanograms/kg/minute adjusted according to response; higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension

Anaphylaxis section 3.4.3

Cardiopulmonary arrest section 2.7.3

Administration for *continuous intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9% and give through a central venous catheter. Incompatible with bicarbonate and alkaline solutions.

Neonatal intensive care, dilute 3 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 100 nanograms/kg/minute

Note These infusions are usually made up with adrenaline 1 in 1000 (1 mg/mL) solution; this concentration of adrenaline is not licensed for intravenous administration

Preparations

Section 3.4.3

2.7.3 Cardiopulmonary resuscitation

The algorithms for cardiopulmonary resuscitation (see inside back cover) reflect the recommendations of the Resuscitation Council (UK); they cover paediatric basic life support, paediatric advanced life support, and newborn life support. The guidelines are available at www.resus.org.uk.

Paediatric advanced life support Cardiopulmonary (cardiac) arrest in children is rare and frequently represents the terminal event of progressive shock or respiratory failure.

During cardiopulmonary arrest in children without intravenous access, the intraosseous route is chosen because it provides rapid and effective response; if circulatory access cannot be gained, the endotracheal tube can be used. When the endotracheal route is used ten times the intravenous dose should be used; the drug should be injected quickly down a narrow bore suction catheter beyond the tracheal end of the tube and then flushed in with 1 or 2 mL of sodium chloride 0.9%. The endotracheal route is useful for lipid-soluble drugs, including lidocaine, adrenaline, atropine, and naloxone. Drugs that are not lipid-soluble (e.g. sodium bicarbonate and calcium chloride) should not be administered by this route because they will injure the airways.

For the management of acute anaphylaxis see section 3.4.3.

2.8 Anticoagulants and protamine

2.8.1 Parenteral anticoagulants

2.8.2 Oral anticoagulants

2.8.3 Protamine sulfate

Although thrombotic episodes are uncommon in childhood, anticoagulants may be required in children with congenital heart disease; in children undergoing haemodialysis; for preventing thrombosis in children requiring chemotherapy and following surgery; and for systemic venous thromboembolism secondary to inherited thrombophilias, systemic lupus erythematosus, or indwelling central venous catheters.

2.8.1 Parenteral anticoagulants

Heparin

Heparin initiates anticoagulation rapidly but has a short duration of action. It is now often referred to as being **standard or unfractionated heparin** to distinguish it from the **low molecular weight heparins** (see p. 114), which have a longer duration of action. For children at high risk of bleeding, unfractionated heparin is more suitable than low molecular weight heparin because its effect can be terminated rapidly by stopping the infusion.

Heparins are used in both the treatment and prophylaxis of thromboembolic disease, mainly to prevent further clotting rather than to lyse existing clots—surgery or a thrombolytic drug may be necessary if a thrombus obstructs major vessels.

Treatment For the initial treatment of thrombotic episodes unfractionated heparin is given as an intravenous loading dose, followed by continuous intravenous infusion (using an infusion pump) or by intermittent subcutaneous injection; the use of intermittent intravenous injection is no longer recommended. Alternatively, a low molecular weight heparin may be given for initial treatment. If an oral anticoagulant (usually warfarin, section 2.8.2) is also required, it may be started at the same time as the heparin (the heparin needs to be continued for at least 5 days and until the INR has been in the therapeutic range for 2 consecutive days). Laboratory monitoring of coagulation activity, preferably on a daily basis, involves determination of the activated partial thromboplastin time (APTT) (for unfractionated heparin only) or of the anti-Factor Xa concentration (for low molecular weight heparins). Local guidelines on recommended APTT for neonates and children should be followed; monitoring of APTT should be discussed with a specialist prior to treatment for thrombotic episodes in neonates.

Prophylaxis Low-dose unfractionated heparin by subcutaneous injection is used to prevent thrombotic episodes in 'high-risk' patients; laboratory monitoring of APTT or anti-Factor Xa concentration is also required in prophylactic regimens in children. Low molecular weight heparins, **aspirin** (section 2.9), and **warfarin** (section 2.8.2) can also be used for prophylaxis.

Pregnancy Heparins are used for the management of thromboembolic disease in pregnancy because they do not cross the placenta. Low molecular weight heparins are preferred because they have a lower risk of osteoporosis and of heparin-induced thrombocytopenia. Low molecular weight heparins are eliminated more rapidly in pregnancy, requiring alteration of the dosage regimen for drugs such as dalteparin, enoxaparin, and tinzaparin. Treatment should be stopped at the onset of labour and advice sought from a specialist on continuing therapy after birth.

Extracorporeal circuits Unfractionated heparin is also used in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.

Haemorrhage If haemorrhage occurs it is usually sufficient to withdraw unfractionated or low molecular weight heparin, but if rapid reversal of the effects of the heparin is required, protamine sulfate (section 2.8.3) is a specific antidote (but only partially reverses the effects of low molecular weight heparins).

HEPARIN

Cautions see notes above; concomitant use of drugs that increase risk of bleeding; **interactions:** Appendix 1 (heparin)

Heparin-induced thrombocytopenia Clinically important heparin-induced thrombocytopenia is immune-mediated and does not usually develop until after 5–10 days; it can be complicated by thrombosis. Platelet counts should be measured just before treatment with unfractionated or low molecular weight heparin, and regular monitoring of platelet counts may be required if given for longer than 4 days¹. Signs of heparin-induced thrombocytopenia include a 30% reduction of platelet count, thrombosis, or skin allergy. If heparin-induced thrombocytopenia is strongly suspected or confirmed, the heparin should be **stopped** and an alternative anticoagulant, such as danaparoid, should be given. Ensure platelet counts return to normal range in those who require warfarin.

Hyperkalaemia Inhibition of aldosterone secretion by unfractionated or low molecular weight heparin can result in hyperkalaemia; patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma-potassium concentration, or those taking potassium-sparing drugs seem to be more susceptible. The risk appears to increase with duration of therapy and plasma-potassium concentration should be measured in children at risk of hyperkalaemia before starting the heparin and monitored regularly thereafter, particularly if treatment is to be continued for longer than 7 days.

Contra-indications haemophilia and other haemorrhagic disorders, thrombocytopenia (including history of heparin-induced thrombocytopenia), recent cerebral haemorrhage, severe hypertension; peptic ulcer; after major trauma or recent surgery to eye or nervous system; acute bacterial endocarditis; spinal or epidural anaesthesia with treatment doses of unfractionated or low molecular weight heparin; hypersensitivity to unfractionated or low molecular weight heparin.

Hepatic impairment risk of bleeding increased—reduce dose or avoid in severe impairment (including oesophageal varices)

Renal impairment risk of bleeding increased in severe impairment—dose may need to be reduced

Pregnancy does not cross the placenta; maternal osteoporosis reported after prolonged use; multidose vials may contain benzyl alcohol—some manufacturers advise avoid; see also notes above

Breast-feeding not excreted in milk due to high molecular weight

Side-effects haemorrhage (see notes above), thrombocytopenia (see Cautions); *rarely* rebound hyperlipidaemia following unfractionated heparin withdrawal, priapism, hyperkalaemia (see Cautions), osteoporosis (risk lower with low molecular weight heparins), alopecia on prolonged use, injection-site reactions, skin necrosis, and hypersensitivity reactions (including urticaria, angioedema, and anaphylaxis)

Licensed use some preparations licensed for use in children

Indications and dose

Maintenance of neonatal umbilical arterial catheter

- By intravenous infusion

Neonate 0.5 units/hour

1. See the British Society for Haematology's Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. *Br J Haematol* 2012; 159: 528–540

Treatment of thrombotic episodes

● By intravenous administration

Neonate initially 75 units/kg (50 units/kg if under 35 weeks corrected gestational age) by intravenous injection, then by continuous intravenous infusion 25 units/kg/hour, adjusted according to APTT

Child 1 month–1 year initially 75 units/kg by intravenous injection, then by continuous intravenous infusion 25 units/kg/hour, adjusted according to APTT

Child 1–18 years initially 75 units/kg by intravenous injection, then by continuous intravenous infusion 20 units/kg/hour, adjusted according to APTT

● By subcutaneous injection

Child 1 month–18 years 250 units/kg twice daily, adjusted according to APTT

Prophylaxis of thrombotic episodes

● By subcutaneous injection

Child 1 month–18 years 100 units/kg (max. 5000 units) twice daily, adjusted according to APTT

Prevention of clotting in extracorporeal circuits
consult product literature**Maintenance of cardiac shunts and critical stents**
consult local protocol

Administration for continuous intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%.
Maintenance of neonatal umbilical arterial catheter, dilute 50 units to a final volume of 50 mL with Sodium Chloride 0.45% or use ready-made bag containing 500 units in 500 mL Sodium Chloride 0.9%; infuse at 0.5 mL/hour.

Neonatal intensive care (treatment of thrombosis), dilute 1250 units/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 1 mL/hour provides a dose of 25 units/kg/hour

Heparin Sodium (Non-proprietary) (PoM)

Injection, heparin sodium 1000 units/mL, net price 1-mL amp = £1.49, 5-mL amp = £3.75, 5-mL vial = £1.53, 10-mL amp = £6.46, 20-mL amp = £4.75; 5000 units/mL, 1-mL amp = £2.90, 5-mL amp = £7.58, 5-mL vial = £6.31; 25 000 units/mL, 0.2-mL amp = £3.74, 1-mL amp = £7.70, 5-mL vial = £11.11

Excipients may include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Heparin Calcium (Non-proprietary) (PoM)

Injection, heparin calcium 25 000 units/mL, net price 0.2-mL amp = £3.91

Low molecular weight heparins

Dalteparin, enoxaparin, and tinzaparin are low molecular weight heparins used for treatment and prophylaxis of thrombotic episodes in children (see also Heparin, p. 113). Their duration of action is longer than that of unfractionated heparin and in adults and older children *once-daily subcutaneous* dosage is sometimes possible; however, younger children require relatively higher doses (possibly due to larger volume of distribution, altered heparin pharmacokinetics, or lower plasma concentrations of antithrombin) and twice daily dosage is

sometimes necessary. Low molecular weight heparins are convenient to use, especially in children with poor venous access. Routine monitoring of anti-Factor Xa activity is not usually required except in neonates; monitoring may also be necessary in severely ill children and those with renal or hepatic impairment.

Haemorrhage See under Heparin.

Hepatic impairment Reduce dose in severe impairment—risk of bleeding may be increased.

Pregnancy Not known to be harmful, low molecular weight heparins do not cross the placenta; see also Heparin, p. 113.

Breast-feeding Due to the relatively high molecular weight of these drugs and inactivation in the gastrointestinal tract, passage into breast-milk and absorption by the nursing infant are likely to be negligible; however manufacturers advise avoid.

DALTEPARIN SODIUM

Cautions see under Heparin and notes above

Contra-indications see under Heparin

Hepatic impairment see notes above

Renal impairment risk of bleeding may be increased—dose reduction and monitoring of anti-Factor Xa may be required; unfractionated heparin may be preferable

Pregnancy see notes above; also multidose vial contains benzyl alcohol—manufacturer advises avoid

Breast-feeding see notes above

Side-effects see under Heparin

Licensed use not licensed for use in children

Indications and dose**Treatment of thrombotic episodes**

● By subcutaneous injection

Neonate 100 units/kg twice daily

Child 1 month–12 years 100 units/kg twice daily

Child 12–18 years 200 units/kg (max. 18 000 units) once daily, if increased risk of bleeding reduced to 100 units/kg twice daily

Treatment of venous thromboembolism in pregnancy

● By subcutaneous injection

Child 12–18 years early pregnancy body-weight under 50 kg, 5000 units twice daily; body-weight 50–70 kg, 6000 units twice daily; body-weight 70–90 kg, 8000 units twice daily; body-weight over 90 kg, 10 000 units twice daily

Prophylaxis of thrombotic episodes

● By subcutaneous injection

Neonate 100 units/kg once daily

Child 1 month–12 years 100 units/kg once daily

Child 12–18 years 2500–5000 units once daily

Fragmin® (Pfizer) (PoM)

Injection (single-dose syringe), dalteparin sodium 12 500 units/mL, net price 2500-unit (0.2-mL) syringe = £1.86; 25 000 units/mL, 5000-unit (0.2-mL) syringe = £2.82, 7500-unit (0.3-mL) syringe = £4.23, 10 000-unit (0.4-mL) syringe = £5.65, 12 500-unit (0.5-mL) syringe = £7.06, 15 000-unit (0.6-mL) syringe = £8.47, 18 000-unit (0.72-mL) syringe = £10.16

Injection, dalteparin sodium 2500 units/mL (for subcutaneous or intravenous use), net price 4-mL (10 000-unit) amp = £5.12; 10 000-units/mL (for subcutaneous or intravenous use), 1-mL (10 000-unit) amp = £5.12; 25 000 units/mL (for subcutaneous use only), 4-mL (100 000-unit) vial = £48.66

Excipients include benzyl alcohol (in 100 000-unit/4 mL multidose vial) (avoid in neonates, see, p. 2)

Injection (graduated syringe), dalteparin sodium 10 000 units/mL, net price 1-mL (10 000-unit) syringe = £5.65

ENOXAPARIN SODIUM

Cautions see under Heparin and notes above

Contra-indications see under Heparin

Hepatic impairment see notes above

Renal impairment risk of bleeding may be increased; reduce dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; monitoring of anti-Factor Xa may be required; unfractionated heparin may be preferable

Pregnancy see notes above; also multidose vial contains benzyl alcohol—avoid

Breast-feeding see notes above

Side-effects see under Heparin

Licensed use not licensed for use in children

Indications and dose

Treatment of thrombotic episodes

- By subcutaneous injection

Neonate 1.5–2 mg/kg twice daily

Child 1–2 months 1.5 mg/kg twice daily

Child 2 months–18 years 1 mg/kg twice daily

Treatment of venous thromboembolism in pregnancy

- By subcutaneous injection

Child 12–18 years early pregnancy body-weight under 50 kg, 40 mg (4000 units) twice daily; body-weight 50–70 kg, 60 mg (6000 units) twice daily; body-weight 70–90 kg, 80 mg (8000 units) twice daily; body-weight over 90 kg, 100 mg (10 000 units) twice daily

Prophylaxis of thrombotic episodes

- By subcutaneous injection

Neonate 750 micrograms/kg twice daily

Child 1–2 months 750 micrograms/kg twice daily

Child 2 months–18 years 500 micrograms/kg twice daily; max. 40 mg daily

Clexane[®] (Sanofi-Aventis) (PoM)

Injection, enoxaparin sodium 100 mg/mL, net price 20-mg (0.2-mL, 2000-units) syringe = £2.27, 40-mg (0.4-mL, 4000-units) syringe = £3.03, 60-mg (0.6-mL, 6000-units) syringe = £4.57, 80-mg (0.8-mL, 8000-units) syringe = £6.49, 100-mg (1-mL, 10 000-units) syringe = £8.03, 300-mg (3-mL, 30 000-units) vial (Clexane[®] Multi-Dose) = £21.33; 150 mg/mL (Clexane[®] Forte), 120-mg (0.8-mL, 12 000-units) syringe = £9.77, 150-mg (1-mL, 15 000-units) syringe = £11.10

Excipients include benzyl alcohol (in 300 mg multidose vials) (avoid in neonates, see, p. 2)

TINZAPARIN SODIUM

Cautions see under Heparin and notes above

Contra-indications see under Heparin

Hepatic impairment see notes above

Renal impairment risk of bleeding may be increased—monitoring of anti-Factor Xa may be required if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; dose reduction may be required if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²; unfractionated heparin may be preferable

Pregnancy see notes above; also vials contain benzyl alcohol—manufacturer advises avoid

Breast-feeding see notes above

Side-effects see under Heparin; also *less commonly* headache

Licensed use not licensed for use in children

Indications and dose

Treatment of thrombotic episodes

- By subcutaneous injection

Child 1–2 months 275 units/kg once daily

Child 2 months–1 year 250 units/kg once daily

Child 1–5 years 240 units/kg once daily

Child 5–10 years 200 units/kg once daily

Child 10–18 years 175 units/kg once daily

Treatment of venous thromboembolism in pregnancy

- By subcutaneous injection

Child 12–18 years 175 units/kg once daily (based on early pregnancy body-weight)

Prophylaxis of thrombotic episodes

- By subcutaneous injection

Child 1 month–18 years 50 units/kg once daily

Innohep[®] (LEO) (PoM)

Injection, tinzaparin sodium 10 000 units/mL, net price 2500-unit (0.25-mL) syringe = £1.98, 3500-unit (0.35-mL) syringe = £2.77, 4500-unit (0.45-mL) syringe = £3.56, 20 000-unit (2-mL) vial = £10.57

Injection, tinzaparin sodium 20 000 units/mL, net price 0.5-mL (10 000-unit) syringe = £8.50, 0.7-mL (14 000-unit) syringe = £11.90, 0.9-mL (18 000-unit) syringe = £15.30, 2-mL (40 000-unit) vial = £34.20

Excipients include benzyl alcohol (in vials) (avoid in neonates, see Excipients, p. 2), sulfites (in 20 000 units/mL vial and syringe)

Heparinoids

Danaparoid is a heparinoid that has a role in children who develop heparin-induced thrombocytopenia, providing they have no evidence of cross-reactivity.

DANAPAROID SODIUM

Cautions recent bleeding or risk of bleeding; concomitant use of drugs that increase risk of bleeding; antibodies to heparins (risk of antibody-induced thrombocytopenia)

Contra-indications haemophilia and other haemorrhagic disorders, thrombocytopenia (unless patient has heparin-induced thrombocytopenia), recent cerebral haemorrhage, severe hypertension, active peptic ulcer (unless this is the reason for operation),

diabetic retinopathy, acute bacterial endocarditis, spinal or epidural anaesthesia with treatment doses of danaparoid

Hepatic impairment caution in moderate impairment (increased risk of bleeding); avoid in severe impairment unless the child has heparin-induced thrombocytopenia and no alternative available

Renal impairment use with caution in moderate impairment; increased risk of bleeding (monitor anti-Factor Xa activity); avoid in severe impairment unless child has heparin-induced thrombocytopenia and no alternative available

Pregnancy manufacturer advises avoid—limited information available but not known to be harmful

Breast-feeding amount probably too small to be harmful but manufacturer advises avoid

Side-effects haemorrhage; hypersensitivity reactions (including rash)

Licensed use not licensed for use in children

Indications and dose

Thromboembolic disease in children with history of heparin-induced thrombocytopenia

• By intravenous administration

Neonate initially 30 units/kg *by intravenous injection* then *by continuous intravenous infusion* 1.2–2 units/kg/hour adjusted according to coagulation activity

Child 1 month–16 years initially 30 units/kg (max. 1250 units if body-weight under 55 kg, 2500 units if over 55 kg) *by intravenous injection* then *by continuous intravenous infusion* 1.2–2 units/kg/hour adjusted according to coagulation activity

Child 16–18 years initially 2500 units (1250 units if body-weight under 55 kg, 3750 units if over 90 kg) *by intravenous injection* then *by continuous intravenous infusion* 400 units/hour for 2 hours, then 300 units/hour for 2 hours, then 200 units/hour for 5 days adjusted according to coagulation activity

Administration for *intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%

Orgaran® (MSD) (PoM)

Injection, danaparoid sodium 1250 units/mL, net price 0.6-mL amp (750 units) = £26.67

Heparin flushes

The use of heparin flushes should be kept to a minimum. For maintaining patency of peripheral venous catheters, sodium chloride 0.9% injection is as effective as heparin flushes. The role of heparin flushes in maintaining patency of arterial and central venous catheters is unclear.

Heparin Sodium (Non-proprietary) (PoM)

Solution, heparin sodium 10 units/mL, net price 5-mL amp = £1.50; 100 units/mL, 2-mL amp = £1.57

Excipients may include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Epoprostenol

Epoprostenol (prostacyclin) can be given to inhibit platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated. For its use in pulmonary hypertension, see section 2.5.1.2. It is a potent

vasodilator and therefore its side-effects include flushing, headache, and hypotension.

2.8.2 Oral anticoagulants

Oral anticoagulants antagonise the effects of vitamin K and take at least 48 to 72 hours for the anticoagulant effect to develop fully; if an immediate effect is required, unfractionated or low molecular weight heparin must be given concomitantly.

Uses Warfarin is the drug of choice for the treatment of systemic thromboembolism in children (not neonates) after initial heparinisation. It may also be used occasionally for the treatment of intravascular or intracardiac thrombi. Warfarin is used prophylactically in those with chronic atrial fibrillation, dilated cardiomyopathy, certain forms of reconstructive heart surgery, mechanical prosthetic heart valves, and some forms of hereditary thrombophilia (e.g. homozygous protein C deficiency).

Unfractionated or a low molecular weight heparin (section 2.8.1) is usually preferred for the prophylaxis of venous thromboembolism in children undergoing surgery; alternatively warfarin can be continued in selected children currently taking warfarin and who are at a high risk of thromboembolism (seek expert advice).

Dose The base-line prothrombin time should be determined but the initial dose should not be delayed whilst awaiting the result.

An induction dose is usually given over 4 days (see under Warfarin Sodium below). The subsequent maintenance dose depends on the prothrombin time, reported as INR (international normalised ratio) and should be taken at the same time each day.

Target INR The following indications and target INRs¹ for adults take into account recommendations of the British Society for Haematology²:

INR 2.5 for:

- treatment of deep-vein thrombosis or pulmonary embolism (including those associated with antiphospholipid syndrome or for recurrence in patients no longer receiving warfarin)
- atrial fibrillation
- cardioversion—target INR should be achieved at least 3 weeks before cardioversion and anticoagulation should continue for at least 4 weeks after the procedure (higher target values, such as an INR of 3, can be used for up to 4 weeks before the procedure to avoid cancellations due to low INR)
- dilated cardiomyopathy
- mitral stenosis or regurgitation in patients with either atrial fibrillation, a history of systemic embolism, a left atrial thrombus, or an enlarged left atrium
- bioprosthetic heart valves in the mitral position (treat for 3 months), or in patients with a history of systemic embolism (treat for at least 3 months), or with a left atrial thrombus at surgery (treat until clot resolves), or with other risk factors (e.g. atrial fibrillation or a low ventricular ejection fraction)

1. An INR which is within 0.5 units of the target value is generally satisfactory; larger deviations require dosage adjustment. Target values (rather than ranges) are now recommended.
2. Guidelines on Oral Anticoagulation with Warfarin—fourth edition. *Br J Haematol* 2011; 154: 311–324.

- acute arterial embolism requiring embolectomy (consider long-term treatment)
- myocardial infarction;

INR 3.5 for:

- recurrent deep-vein thrombosis or pulmonary embolism in patients currently receiving anticoagulation with INR above 2;

Mechanical prosthetic heart valves:

- the recommended target INR depends on the type and location of the valve, and patient-related risk factors
- consider increasing the INR target, or adding an antiplatelet drug, if an embolic event occurs whilst anticoagulated at the target INR.

Monitoring It is essential that the INR be determined daily or on alternate days in early days of treatment, *then* at longer intervals (depending on response¹) *then* up to every 12 weeks.

Haemorrhage The main adverse effect of all oral anticoagulants is haemorrhage. Checking the INR and omitting doses when appropriate is essential; if the anticoagulant is stopped but not reversed, the INR should be measured 2–3 days later to ensure that it is falling. The cause of an elevated INR should be investigated. The following recommendations (which take into account the recommendations of the British Society for Haematology²) are based on the result of the INR and whether there is major or minor bleeding; the recommendations apply to **adults** taking warfarin:

- Major bleeding—stop warfarin; give phytonadione (vitamin K₁) 5 mg by slow intravenous injection; give dried prothrombin complex (factors II, VII, IX, and X—section 2.11) 25–50 units/kg (if dried prothrombin complex unavailable, fresh frozen plasma 15 mL/kg can be given but is less effective); recombinant factor VIIa is not recommended for emergency anticoagulation reversal
- INR > 8.0, minor bleeding—stop warfarin; give phytonadione (vitamin K₁) 1–3 mg by slow intravenous injection; repeat dose of phytonadione if INR still too high after 24 hours; restart warfarin when INR < 5.0
- INR > 8.0, no bleeding—stop warfarin; give phytonadione (vitamin K₁) 1–5 mg by mouth (unlicensed use); repeat dose of phytonadione if INR still too high after 24 hours; restart warfarin when INR < 5.0
- INR 5.0–8.0, minor bleeding—stop warfarin; give phytonadione (vitamin K₁) 1–3 mg by slow intravenous injection; restart warfarin when INR < 5.0
- INR 5.0–8.0, no bleeding—withhold 1 or 2 doses of warfarin and reduce subsequent maintenance dose
- Unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology

1. Change in child's clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. See also **interactions**, Appendix 1 (warfarin). Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect warfarin control.

2. Guidelines on Oral Anticoagulation with Warfarin—fourth edition. *Br J Haematol* 2011; 154: 311–324.

Pregnancy Oral anticoagulants are teratogenic and should not be given in the first trimester of pregnancy. Adolescents at risk of pregnancy should be warned of this danger since stopping warfarin before the sixth week of gestation may largely avoid the risk of fetal abnormality. Oral anticoagulants cross the placenta with risk of congenital malformations, and placental, fetal, or neonatal haemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, oral anticoagulants should be avoided in pregnancy, especially in the first and third trimesters. Difficult decisions may have to be made, particularly in those with prosthetic heart valves or with a history of recurrent venous thrombosis, pulmonary embolism, or atrial fibrillation.

Babies of mothers taking warfarin at the time of delivery need to be offered immediate prophylaxis with at least 100 micrograms/kg of intramuscular phytonadione (vitamin K₁), see section 9.6.6

Breast-feeding With warfarin, there is a risk of haemorrhage which is increased by vitamin-K deficiency. Warfarin is not present in milk in significant amounts and appears safe.

Dietary differences Infant formula is supplemented with vitamin K, which makes formula-fed infants resistant to warfarin; they may therefore need higher doses. In contrast breast milk contains low concentrations of vitamin K making breast-fed infants more sensitive to warfarin.

Treatment booklets Anticoagulant treatment booklets should be issued to children or their carers; these booklets include advice for children or their carers on anticoagulant treatment, an alert card to be carried by the patient at all times, and a section for recording of INR results and dosage information. In **England, Wales, and Northern Ireland**, they are available for purchase from:

3M Security Print and Systems Limited
Gorse Street, Chadderton
Oldham,
OL9 9QH
Tel: 0845 610 1112

GP practices can obtain supplies through their Local Area Team stores. NHS Trusts can order supplies from www.nhsforms.co.uk or by emailing nhsforms@mmm.com.

In **Scotland**, treatment booklets and starter information packs can be obtained by emailing stockorders.dppas@apsgroup.co.uk.

Electronic copies of the booklets and further advice are also available at www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/anticoagulant.

WARFARIN SODIUM

Cautions see notes above; also conditions in which risk of bleeding is increased, e.g. history of gastrointestinal bleeding, peptic ulcer, recent surgery, recent ischaemic stroke, postpartum (delay warfarin until risk of haemorrhage is low—usually 5–7 days after delivery), bacterial endocarditis (use only if warfarin otherwise indicated); uncontrolled hypertension; concomitant use of drugs that increase risk of bleeding; avoid cranberry juice; **interactions**: Appendix 1 (warfarin)

Contra-indications haemorrhagic stroke; significant bleeding; avoid use within 48 hours postpartum

Hepatic impairment avoid in severe impairment, especially if prothrombin time already prolonged

Renal impairment use with caution in mild to moderate impairment; monitor INR more frequently in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects haemorrhage—see notes above; also nausea, vomiting, diarrhoea, jaundice, hepatic dysfunction, pancreatitis, pyrexia, alopecia, purpura, rash, 'purple toes', skin necrosis (increased risk in patients with protein C or protein S deficiency)

Licensed use not licensed for use in children

Indications and dose

Treatment and prophylaxis of thrombotic episodes

• By mouth

Neonate (under specialist advice) 200 micrograms/kg as a single dose on first day, reduced to 100 micrograms/kg once daily for following 3 days (but if INR still below 1.4 use 200 micrograms/kg once daily, or if INR above 3 use 50 micrograms/kg once daily, if INR above 3.5 omit dose); then adjusted according to INR, usual maintenance 100–300 micrograms/kg once daily (may need up to 400 micrograms/kg once daily especially if bottle fed—see notes above)

Child 1 month–18 years 200 micrograms/kg (max. 10 mg) as a single dose on first day, reduced to 100 micrograms/kg (max. 5 mg) once daily for following 3 days (but if INR still below 1.4 use 200 micrograms/kg (max. 10 mg) once daily, or if INR above 3 use 50 micrograms/kg (max. 2.5 mg) once daily, or if INR above 3.5 omit dose); then adjusted according to INR, usual maintenance 100–300 micrograms/kg once daily (may need up to 400 micrograms/kg once daily especially if bottle fed—see notes above)

Note Induction dose may need to be altered according to condition (e.g. abnormal liver function tests, cardiac failure), concomitant interacting drugs, and if baseline INR above 1.3

Warfarin (Non-proprietary) (PoM)

Tablets, warfarin sodium 500 micrograms (white), net price 28-tab pack = £1.29; 1 mg (brown), 28-tab pack = 83p; 3 mg (blue), 28-tab pack = 88p; 5 mg (pink), 28-tab pack = 91p. Label: 10, anticoagulant card

Brands include Marevan®

Oral suspension, warfarin sodium 1 mg/mL, net price 150-mL = £90.00. Label: 10, anticoagulant card

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

2.8.3 Protamine sulfate

Protamine sulfate is used to treat overdosage of unfractionated or low molecular weight heparin. The long half-life of low molecular weight heparins should be taken into consideration when determining the dose of protamine sulfate; the effects of low molecular weight heparins can persist for up to 24 hours after administration. Excessive doses of protamine sulfate can have an anticoagulant effect.

PROTAMINE SULFATE

Cautions see above; also monitor activated partial thromboplastin time or other appropriate blood clotting parameters; if increased risk of allergic reaction to protamine (includes previous treatment with protamine or protamine insulin, allergy to fish, and adolescent males who are infertile)

Side-effects nausea, vomiting, lassitude, flushing, hypotension, hypertension, bradycardia, dyspnoea, rebound bleeding, back pain; hypersensitivity reactions (including angioedema, anaphylaxis) and pulmonary oedema reported

Indications and dose

Overdosage with intravenous injection or intravenous infusion of unfractionated heparin

- By intravenous injection (rate not exceeding 5 mg/minute)

Child 1 month–18 years to neutralise each 100 units of unfractionated heparin, 1 mg if less than 30 minutes lapsed since overdose, 500–750 micrograms if 30–60 minutes lapsed, 750–500 micrograms if 60–120 minutes lapsed, 250–375 micrograms if over 120 minutes lapsed; max. 50 mg

Overdosage with subcutaneous injection of unfractionated heparin

- By intravenous injection and intravenous infusion

Child 1 month–18 years 1 mg neutralises approx. 100 units of unfractionated heparin; give 50–100% of the total dose by *intravenous injection* (rate not exceeding 5 mg/minute), then give any remainder of dose by *intravenous infusion* over 8–16 hours; max. total dose 50 mg

Overdosage with subcutaneous injection of low molecular weight heparin

- By intermittent intravenous injection (rate not exceeding 5 mg/minute) or by continuous intravenous infusion

Child 1 month–18 years 1 mg neutralises approx. 100 units low molecular weight heparin (consult product literature of low molecular weight heparin for details); max. 50 mg

Administration may be diluted if necessary with Sodium Chloride 0.9%

Protamine Sulfate (Non-proprietary) (PoM)

Injection, protamine sulfate 10 mg/mL, net price 5-mL amp = £1.14, 10-mL amp = £3.96

2.9 Antiplatelet drugs

Antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation in the arterial circulation, because in faster-flowing vessels, thrombi are composed mainly of platelets with little fibrin.

Aspirin has limited use in children because it has been associated with Reye's syndrome. Aspirin-containing preparations should not be given to children and adolescents under 16 years, unless specifically indicated, such as for Kawasaki disease (see below), for prophylaxis of clot formation after cardiac surgery, or for prophylaxis of stroke in children at high risk.

If aspirin causes dyspepsia, or if the child is at a high risk of gastro-intestinal bleeding, a proton pump inhibitor

(section 1.3.5) or a H₂-receptor antagonist (section 1.3.1) can be added.

Dipyridamole is also used as an antiplatelet drug to prevent clot formation after cardiac surgery and may be used with specialist advice for treatment of persistent coronary artery aneurysms in Kawasaki disease.

Kawasaki disease Initial treatment is with high-dose aspirin and a single dose of intravenous normal immunoglobulin (p. 628); this combination has an additive anti-inflammatory effect resulting in faster resolution of fever and a decreased incidence of coronary artery complications. After the acute phase, when the patient is afebrile, aspirin is continued at a lower dose to prevent coronary artery abnormalities.

ASPIRIN (antiplatelet) (Acetylsalicylic Acid)

Cautions asthma; uncontrolled hypertension; previous peptic ulceration (but manufacturers may advise avoidance of low-dose aspirin in history of peptic ulceration); concomitant use of drugs that increase risk of bleeding; G6PD deficiency (section 9.1.5); dehydration; **interactions:** Appendix 1 (aspirin)

Contra-indications children under 16 years (risk of Reye's syndrome) unless for indications below; active peptic ulceration; haemophilia and other bleeding disorders

Hypersensitivity Aspirin and other NSAIDs are **contra-indicated** in history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID

Hepatic impairment avoid in severe impairment—increased risk of gastro-intestinal bleeding

Renal impairment use with caution (avoid in severe impairment); sodium and water retention; deterioration in renal function; increased risk of gastro-intestinal bleeding

Pregnancy use with caution during third trimester; impaired platelet function and risk of haemorrhage; delayed onset and increased duration of labour with increased blood loss; avoid analgesic doses if possible in last few weeks (low doses probably not harmful); with high doses, closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension of newborn; kernicterus in jaundiced neonates

Breast-feeding avoid—possible risk of Reye's syndrome; regular use of high doses could impair platelet function and produce hypoprothrombinaemia in infant if neonatal vitamin K stores low

Side-effects bronchospasm; gastro-intestinal haemorrhage (occasionally major), also other haemorrhage (e.g. subconjunctival)

Licensed use not licensed for use in children under 16 years

Indications and dose

Kawasaki disease

• By mouth

Neonate initially 8 mg/kg 4 times daily for 2 weeks or until afebrile, followed by 5 mg/kg once daily for 6–8 weeks; if no evidence of coronary lesions after 8 weeks, discontinue treatment or seek expert advice

Child 1 month–12 years initially 7.5–12.5 mg/kg 4 times daily for 2 weeks or until afebrile, then 2–5 mg/kg once daily for 6–8 weeks; if no evidence

of coronary lesions after 8 weeks, discontinue treatment or seek expert advice

Antiplatelet, prevention of thrombus formation after cardiac surgery

• By mouth

Neonate 1–5 mg/kg once daily

Child 1 month–12 years 1–5 mg/kg (usual max. 75 mg) once daily

Child 12–18 years 75 mg once daily

Aspirin (Non-proprietary) (PoM)

Dispersible tablets, aspirin 75 mg, net price 28 = £74p; 300 mg, 100-tab pack = £3.19. Label: 13, 21, 32
Tablets, e/c, aspirin 75 mg, net price 28-tab pack = £79p; 56-tab pack = £1.70; 300 mg, 100-tab pack = £11.90. Label: 5, 25, 32

Brands include *Caprin*[®], *Micropirin*[®]

Suppositories, available from 'special-order' manufacturers or specialist importing companies, see p. 840

Nu-Seals[®] Aspirin (Alliance) (PoM)

Tablets, e/c, aspirin 75 mg, net price 56-tab pack = £3.12; 300 mg, 100-tab pack = £4.15. Label: 5, 25, 32

DIPYRIDAMOLE

Cautions aortic stenosis, left ventricular outflow obstruction, heart failure; may exacerbate migraine; hypotension; myasthenia gravis (risk of exacerbation); concomitant use of drugs that increase risk of bleeding; coagulation disorders; **interactions:** Appendix 1 (dipyridamole)

Pregnancy not known to be harmful

Breast-feeding manufacturers advise use only if essential—small amount present in milk

Side-effects gastro-intestinal effects, dizziness, myalgia, throbbing headache, hypotension, hot flushes and tachycardia; hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angioedema; increased bleeding during or after surgery; thrombocytopenia reported

Licensed use not licensed for use in children

Indications and dose

Kawasaki disease

• By mouth

Child 1 month–12 years 1 mg/kg 3 times daily

Prevention of thrombus formation after cardiac surgery

• By mouth

Child 1 month–12 years 2.5 mg/kg twice daily

Child 12–18 years 100–200 mg 3 times daily

Administration injection solution can be given orally

Dipyridamole (Non-proprietary) (PoM)

Tablets, coated, dipyridamole 25 mg, net price 84 = £2.68; 100 mg, 84 = £3.46. Label: 22

Oral suspension, dipyridamole 50 mg/5 mL, net price 150 mL = £39.41

Persantin[®] (Boehringer Ingelheim) (PoM)

Tablets, s/c, dipyridamole, 100 mg, net price 84-tab pack = £6.30. Label: 22

Injection, dipyridamole 5 mg/mL, net price 2-mL amp = 16p

2.10 Myocardial infarction and fibrinolysis

2.10.1 Management of myocardial infarction

2.10.2 Fibrinolytic drugs

2.10.1 Management of myocardial infarction

This section is not included in *BNF for Children*.

2.10.2 Fibrinolytic drugs

Fibrinolytic drugs act as thrombolytics by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

Alteplase, streptokinase, and urokinase are used in children to dissolve intravascular thrombi and unblock occluded arteriovenous shunts, catheters, and indwelling central lines blocked with fibrin clots. Treatment should be started as soon as possible after a clot has formed and discontinued once a pulse in the affected limb is detected, or the shunt or catheter unblocked.

The safety and efficacy of treatment remains uncertain, especially in neonates. A fibrinolytic drug is probably only appropriate where arterial occlusion threatens ischaemic damage; an anticoagulant may stop the clot getting bigger. Alteplase is the preferred fibrinolytic in children and neonates; there is less risk of adverse effects including allergic reactions.

Cautions Thrombolytic drugs should be used with caution if there is a risk of bleeding including that from venepuncture or invasive procedures. They should also be used with caution in conditions with an increased risk of haemorrhage, or where there has been recent or concomitant use of drugs that increase the risk of bleeding.

Contra-indications Thrombolytic drugs are contra-indicated in recent haemorrhage, trauma, or surgery (including dental extraction), coagulation defects, bleeding diatheses, severe hypertension, arteriovenous malformation, aneurysm, neoplasm with risk of haemorrhage, pericarditis, bacterial endocarditis, and acute pancreatitis.

Prolonged persistence of antibodies to streptokinase can reduce the effectiveness of subsequent treatment; therefore, streptokinase should not be used again beyond 4 days of first administration. Streptokinase should also be avoided in children who have had streptococcal infection in the last 12 months.

Hepatic impairment Thrombolytic drugs should be avoided in severe hepatic impairment as there is an increased risk of bleeding.

Pregnancy Thrombolytic drugs can possibly lead to premature separation of the placenta in the first 18 weeks of pregnancy. There is also a risk of maternal haemorrhage throughout pregnancy and post-partum, and also a theoretical risk of fetal haemorrhage throughout pregnancy.

Side-effects Side-effects of thrombolytics are mainly bleeding, nausea, and vomiting. Reperfusion can cause cerebral and pulmonary oedema. Hypotension can also

occur and can usually be controlled by elevating the patient's legs, or by reducing the rate of infusion or stopping it temporarily. Back pain, fever, and convulsions have been reported. Bleeding is usually limited to the site of injection, but intracerebral haemorrhage or bleeding from other sites can occur. Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and anti-fibrinolytic drugs (e.g. tranexamic acid). Thrombolytics can cause allergic reactions (including rash, flushing and urticaria) and anaphylaxis has been reported (for details of management see Allergic Emergencies, section 3.4.3). Guillain-Barré syndrome has been reported rarely after streptokinase treatment.

ALTEPLASE

(rt-PA, tissue-type plasminogen activator)

Cautions see notes above

Contra-indications see notes above; also hypersensitivity to gentamicin (residue from manufacturing process); recent ulcerative gastro-intestinal disease; oesophageal varices; stroke; concomitant treatment with oral anticoagulants; recent delivery

Hepatic impairment see notes above

Pregnancy see notes above

Side-effects see notes above; also risk of cerebral bleeding increased in acute stroke

Licensed use *Actilyse*® not licensed for use in children

Indications and dose

See under preparations, below

Actilyse® (Boehringer Ingelheim) (PoM)

Injection, powder for reconstitution, alteplase 10 mg (5.8 million units)/vial, net price per vial (with diluent) = £144.00; 20 mg (11.6 million units)/vial (with diluent and transfer device) = £216.00; 50 mg (29 million units)/vial (with diluent and transfer device) = £360.00

Dose

Intravascular thrombosis doses may vary—consult local guidelines

• **By intravenous infusion**

Neonate 100–500 micrograms/kg/hour for 3–6 hours; use ultrasound assessment to monitor effect before considering a second course of treatment

Child 1 month–18 years 100–500 micrograms/kg/hour for 3–6 hours; max. 100 mg total daily dose; use ultrasound assessment to monitor effect before considering a second course of treatment

Administration for *intravenous infusion*, dissolve in Water for Injections to a concentration of 1 mg/mL or 2 mg/mL and infuse intravenously; alternatively dilute further in Sodium Chloride 0.9% to a concentration of not less than 200 micrograms/mL; not to be diluted in Glucose

Actilyse Cathflo® (Boehringer Ingelheim) (PoM)

Injection, powder for reconstitution, alteplase 2 mg (1.16 million units)/vial, net price vial (with diluent) = £45.00

Dose

Thrombolytic treatment of occluded central venous access devices (including those used for haemodialysis) consult product literature

STREPTOKINASE

Cautions see notes above; also cerebrovascular disease; mitral valve defect; atrial fibrillation; septic thrombotic disease; cavernous pulmonary disease; recent delivery or abortion

Contra-indications see notes above; also concomitant treatment with oral anticoagulants

Hepatic impairment see notes above

Pregnancy see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 18 years

Indications and dose

Intravascular thrombosis

- By intravenous infusion

Child 1 month–12 years initially 2500–4000 units/kg over 30 minutes, followed by *continuous intravenous infusion* of 500–1000 units/kg/hour for up to 3 days until reperfusion occurs

Child 12–18 years initially 250 000 units over 30 minutes, followed by *continuous intravenous infusion* of 100 000 units/hour for up to 3 days until reperfusion occurs

Administration reconstitute with Sodium Chloride 0.9%, then dilute further with Glucose 5% or Sodium Chloride 0.9% after reconstitution. Monitor fibrinogen concentration closely; if fibrinogen concentration less than 1 g/litre, stop streptokinase infusion and start unfractionated heparin; restart streptokinase once fibrinogen concentration reaches 1 g/litre

Streptase[®] (CSL Behring) (PoM)

Injection, powder for reconstitution, streptokinase, net price 250 000-unit vial = £13.52; 1.5 million-unit vial = £70.92 (hosp. only)

UROKINASE

Cautions see notes above; also severe cerebrovascular disease; mitral valve defect; atrial fibrillation; septic thrombotic disease; cavernous pulmonary disease; recent delivery

Contra-indications see notes above; also recent stroke; concomitant treatment with oral anticoagulants or heparin

Hepatic impairment see notes above

Pregnancy see notes above

Side-effects see notes above

Indications and dose

Occluded arteriovenous shunts, catheters, and indwelling central lines

- By injection directly into catheter or central line

Neonate 5000–25 000 units in sodium chloride 0.9% to fill catheter dead-space **only**; leave for 20–60 minutes then aspirate the lysate; flush with sodium chloride 0.9%

Child 1 month–18 years 5000–25 000 units in sodium chloride 0.9% to fill catheter dead-space **only**; leave for 20–60 minutes then aspirate the lysate; flush with sodium chloride 0.9%

Administration may be diluted, after reconstitution, with Sodium Chloride 0.9%

Urokinase (Non-Proprietary) (PoM)

Injection, powder for reconstitution, urokinase, net price 10 000-unit vial = £33.79; 50 000-unit vial = £69.70; 100 000-unit vial = £106.17; 250 000-unit vial = £185.65; 500 000-unit vial = £365.00

Syner-KINASE[®] (Syner-Med) (PoM)

Injection, powder for reconstitution, urokinase, net price 10 000-unit vial = £35.95; 25 000-unit vial = £45.95; 100 000-unit vial = £112.95

2.11 Antifibrinolytic drugs and haemostatics

Fibrin dissolution can be impaired by the administration of **tranexamic acid**, which inhibits fibrinolysis. It can be used to prevent bleeding or treat bleeding associated with excessive fibrinolysis (e.g. in surgery, dental extraction, obstetric disorders, and traumatic hyphaema) and in the management of menorrhagia; it may also be used in hereditary angioedema (section 3.4.3), epistaxis, and thrombolytic overdose. Tranexamic acid can also be used in cardiac surgery to reduce blood loss and to reduce the need for use of blood products.

Desmopressin (section 6.5.2) is used in the management of mild to moderate haemophilia and von Willebrands' disease. It is also used for testing fibrinolytic response.

TRANEXAMIC ACID

Cautions massive haematuria (avoid if risk of ureteric obstruction); before initiating treatment for menorrhagia, exclude structural or histological causes or fibroids causing distortion of uterine cavity; irregular menstrual bleeding (establish cause before initiating therapy); patients receiving oral contraceptives (increased risk of thrombosis); regular liver function tests in long-term treatment of hereditary angioedema

Contra-indications thromboembolic disease; fibrinolytic conditions following disseminated intravascular coagulation (unless predominant activation of fibrinolytic system with severe bleeding); history of convulsions

Renal impairment reduce dose in mild to moderate impairment; avoid in severe impairment

Pregnancy no evidence of teratogenicity in *animal* studies; manufacturer advises use only if potential benefit outweighs risk—crosses the placenta

Breast-feeding small amount present in milk—antifibrinolytic effect in infant unlikely

Side-effects nausea, vomiting, diarrhoea (reduce dose); less commonly dermatitis; rarely thromboembolic events, visual disturbances including impairment of colour vision (discontinue); *also reported* malaise and hypotension on rapid intravenous injection, convulsions (usually with high doses)

Licensed use not licensed for reduction of blood loss during cardiac surgery; injection not licensed for use in children under 1 year or for administration by intravenous infusion

Indications and dose**Inhibition of fibrinolysis, hereditary angioedema**

• By mouth

Child 1 month–18 years 15–25 mg/kg (max. 1.5 g)
2–3 times daily

• By intravenous injection over at least 10 minutes

Child 1 month–18 years 10 mg/kg (max. 1 g) 2–3
times daily

• By continuous intravenous infusion

Child 1 month–18 years 45 mg/kg over 24 hours

Prevention of excessive bleeding after dental procedures (e.g. in haemophilia)

• By intravenous injection pre-operatively

Child 6–18 years 10 mg/kg (max. 1.5 g)

• By mouth pre-operatively

Child 6–18 years 15–25 mg/kg (max. 1.5 g)

• By mouth postoperatively

Child 6–18 years 15–25 mg/kg (max. 1.5 g) 2–3
times daily for up to 8 days

• Mouthwash 5% solution (specialist use only)

Child 6–18 years rinse mouth with 5–10 mL 4
times daily for 2 days; not to be swallowed

Note Mouthwash available only as extemporaneously
prepared preparation, see Extemporaneous
Preparations, p. 6

Menorrhagia

• By mouth

Child 12–18 years 1 g 3 times daily for up to 4
days; max. 4 g daily (initiate when menstruation
has started)

Reduction of blood loss during cardiac surgery
consult local protocol

Administration for intravenous administration, dilute
with Glucose 5% or Sodium Chloride 0.9%

Tranexamic acid (Non-proprietary) (PoM)

Tablets, tranexamic acid 500 mg, net price 60-tab
pack = £6.23

Injection, tranexamic acid 100 mg/mL, net price
5-mL amp = £1.50 (hosp. only)

Cyklokapron® (Meda) (PoM)

Tablets, f/c, scored, tranexamic acid 500 mg, net
price 60-tab pack = £14.30

Cyklokapron® (Pfizer) (PoM)

Injection, tranexamic acid 100 mg/mL, net price
5-mL amp = £1.55

Blood products

These products should be used on the advice of a
haematologist.

DRIED PROTHROMBIN COMPLEX
(Human Prothrombin Complex)

Dried prothrombin complex is prepared from human plasma
by a suitable fractionation technique, and contains factor IX,
together with variable amounts of factors II, VII, and X

Cautions risk of thrombosis; disseminated intravas-
cular coagulation; history of myocardial infarction or
coronary heart disease; postoperative use; vaccina-
tion against hepatitis A (p. 612) and hepatitis B
(p. 614) may be required

Contra-indications angina; recent myocardial infar-
ction (except in life-threatening haemorrhage following
overdosage of oral anticoagulants, and before induc-
tion of fibrinolytic therapy); history of heparin-
induced thrombocytopenia

Hepatic impairment monitor closely (risk of throm-
boembolic complications)

Side-effects thrombotic events (including dissemi-
nated intravascular coagulation); rarely headache; very
rarely pyrexia, antibody formation, hypersensitivity
reactions (including anaphylaxis); nephrotic
syndrome also reported

Indications and dose

**Treatment and peri-operative prophylaxis of
haemorrhage in congenital deficiency of factors II,
VII, IX, or X if purified specific coagulation factors
not available, treatment and peri-operative
prophylaxis of haemorrhage in acquired defi-
ciency of factors II, VII, IX, or X (e.g. during warf-
arin treatment—see section 2.8.2)**

Consult haematologist

Available from CSL Behring (*Beriplex® P/N*), Octapharma
(*Octaplex®*)

FACTOR VIIa (RECOMBINANT)
Eptacog alfa (activated)

Cautions risk of thrombosis or disseminated intra-
vascular coagulation

Side-effects very rarely nausea, thrombotic events
(including myocardial infarction and cerebrovascular
accident), coagulation disorders, fever, pain, and
allergic reactions including rash

Indications and dose

**Treatment and prophylaxis of haemorrhage in
haemophilia A or B with inhibitors to factors VIII
or IX, acquired haemophilia, factor VII deficiency,
or Glanzmann's thrombasthenia**

Consult haematologist

Available from Novo Nordisk (*NovoSeven®*)

FACTOR VIII FRACTION, DRIED
(Human Coagulation Factor VIII, Dried)

Dried factor VIII fraction is prepared from human plasma by
a suitable fractionation technique; it may also contain varying
amounts of von Willebrand factor

Cautions monitor for development of factor VIII
inhibitors; intravascular haemolysis after large or
frequently repeated doses in patients with blood
groups A, B, or AB—less likely with high potency
concentrates; vaccination against hepatitis A (p. 612)
and hepatitis B (p. 614) may be required (not neces-
sary with recombinant preparation)

Side-effects gastro-intestinal disturbances, taste dis-
turbances; flushing, palpitation; dyspnoea, coughing;
headache, dizziness, paraesthesia, drowsiness;
blurred vision; antibody formation; hypersensitivity
reactions including hypotension, angioedema, chills,
fever, urticaria, and anaphylaxis

Indications and dose

**Treatment and prophylaxis of haemorrhage in
congenital factor VIII deficiency (haemophilia A),
acquired factor VIII deficiency, or von Wille-
brand's disease**

Consult haematologist

Available from Biotest UK (*Haemoctin®*), CSL Behring
(*Haemate® P*), BPL (*Optivate®*, *8Y®*), Grifols (*Alphanate®*,
Fanhd®), Octapharma (*Octanate®*, *Wilate®*), Haemoctin®

Optivate®, *Fanhti*®, and *Octanate*® are not indicated for use in von Willebrand's disease

Note Preparation of recombinant human coagulation factor VIII (octocog alfa) available from CSL Behring (*Helixate*® *NexGen*), Baxter (*Advate*®), Bayer (*Kogenate*® *Bayer*); preparation of recombinant human coagulation factor VIII (morococog alfa) available from Wyeth (*ReFacto AF*®); octocog alfa and morococog alfa are not indicated for use in von Willebrand's disease

FACTOR VIII INHIBITOR BYPASSING FRACTION

Preparations with factor VIII inhibitor bypassing activity are prepared from human plasma

Cautions vaccination against hepatitis A (p. 612) and hepatitis B (p. 614) may be required

Contra-indications disseminated intravascular coagulation

Side-effects thrombosis, disseminated intravascular coagulation, myocardial infarction; paraesthesia; pyrexia; hypersensitivity reactions including hypotension, flushing, urticaria, rash, and anaphylaxis

Indications and dose

Treatment and prophylaxis of haemorrhage in congenital factor VIII deficiency (haemophilia A) and factor VIII inhibitors; treatment of haemorrhage in non-haemophilic children with acquired factor VIII inhibitors

Consult haematologist

Available from Baxter (*FEIBA*®)

FACTOR IX FRACTION, DRIED

Dried factor IX fraction is prepared from human plasma by a suitable fractionation technique; it may also contain clotting factors II, VII, and X

Cautions risk of thrombosis—principally with former low purity products; vaccination against hepatitis A (p. 612) and hepatitis B (p. 614) may be required (not necessary with recombinant preparation)

Contra-indications disseminated intravascular coagulation

Side-effects gastro-intestinal disturbances; headache, dizziness; allergic reactions including chills, fever

Indications and dose

Treatment and prophylaxis of haemorrhage in congenital factor IX deficiency (haemophilia B)

Consult haematologist

Available from CSL Behring (*Mononine*®), BPL (*Replene*® *VF*, Dried Factor IX Fraction), Grifols (*AlphaNine*®), Biotest UK (*Haemonine*®)

Note Preparation of recombinant coagulation factor IX (nonacog alfa) available from Pfizer (*BeneFIX*®)

FACTOR XIII FRACTION, DRIED (Human Fibrin-stabilising Factor, Dried)

Cautions vaccination against hepatitis A (p. 612) and hepatitis B (p. 614) may be required

Side-effects rarely allergic reactions and fever

Indications and dose

Congenital factor XIII deficiency

Consult haematologist

Available from CSL Behring (*Fibrogammin*® *P*)

FIBRINOGEN, DRIED (Human Fibrinogen)

Fibrinogen is prepared from human plasma

Cautions risk of thrombosis

Pregnancy manufacturer advises not known to be harmful—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects rarely fever, allergic reactions; very rarely thromboembolic events (including myocardial infarction and pulmonary embolism)

Indications and dose

Treatment of haemorrhage in congenital hypofibrinogenaemia or afibrinogenaemia

Consult haematologist

Available from CSL Behring (*Riastap*®)

FRESH FROZEN PLASMA

Fresh frozen plasma is prepared from the supernatant liquid obtained by centrifugation of one donation of whole blood

Cautions need for compatibility; cardiac decompensation; pulmonary oedema; severe protein S deficiency (avoid products with low protein S activity e.g. *OctaplasLG*®); vaccination against hepatitis A (p. 612) and hepatitis B (p. 614) may be required

Contra-indications avoid use as a volume expander; IgA deficiency with confirmed antibodies to IgA

Side-effects nausea, rash, pruritus; less commonly vomiting, oedema; rarely tachycardia, agitation, allergic reactions (including chills, fever, bronchospasm, cardiorespiratory collapse); very rarely arrhythmia, thromboembolism, hypertension

Indications and dose

Replacement of coagulation factors or other plasma proteins where their concentration or functional activity is critically reduced

Consult haematologist

Available from Regional Blood Transfusion Services

Note Children under 16 years should only receive virucidally inactivated preparations of fresh frozen plasma, sourced from 'low prevalence BSE regions' such as the USA

Note A preparation of solvent/detergent treated human plasma (frozen) from pooled donors is available from Octapharma (*OctaplasLG*®)

PROTEIN C CONCENTRATE

Protein C is prepared from human plasma

Cautions hypersensitivity to heparins; vaccination against hepatitis A (p. 612) and hepatitis B (p. 614) may be required

Side-effects very rarely fever, bleeding, dizziness, and hypersensitivity reactions

Indications and dose

Congenital protein C deficiency

Consult haematologist

Available from Baxter (*Ceprotrin*®)

2.12 Lipid-regulating drugs

Atherosclerosis begins in childhood and raised serum-cholesterol in children is associated with cardiovascular disease in adulthood. Lowering the cholesterol, without hindering growth and development in children and adolescents, should reduce the risk of cardiovascular disease in later life.

The risk factors for developing cardiovascular disease include raised serum cholesterol concentration, smoking, hypertension, impaired glucose tolerance, male sex, ethnicity, obesity, triglyceride concentration,

chronic kidney disease, and a family history of cardiovascular disease. Heterozygous familial hypercholesterolaemia is the most common cause of raised serum cholesterol in children; homozygous familial hypercholesterolaemia is very rare and its specialised management is not covered in *BNF for Children*. Familial hypercholesterolaemia can lead to a greater risk of early coronary heart disease and should be managed by a specialist.

Secondary causes of hypercholesterolaemia should be addressed, these include obesity, diet, diabetes mellitus, hypothyroidism (see below), nephrotic syndrome, obstructive biliary disease, glycogen storage disease, and drugs such as corticosteroids.

Management The aim of management of hypercholesterolaemia is to reduce the risk of atherosclerosis while ensuring adequate growth and development. Children with hypercholesterolaemia (or their carers) should receive advice on appropriate lifestyle changes such as improved diet, increased exercise, weight reduction, and not smoking; hypertension should also be managed appropriately (section 2.5). Drug therapy may also be necessary and is discussed below.

Hypothyroidism Children with hypothyroidism should receive adequate thyroid replacement therapy before their requirement for lipid-regulating treatment is assessed because correction of hypothyroidism itself may resolve the lipid abnormality. Untreated hypothyroidism increases the risk of myositis with lipid-regulating drugs.

Drug treatment in heterozygous familial hypercholesterolaemia Lifestyle modifications alone are unlikely to lower cholesterol concentration adequately in heterozygous familial hypercholesterolaemia and drug treatment is often required. Lipid-regulating drugs should be considered by the age of 10 years. The decision to initiate drug treatment will depend on the child's age, the age of onset of coronary heart disease within the family, and the presence of other cardiovascular risk factors. In children with a family history of coronary heart disease in early adulthood, drug treatment before the age of 10 years, and a combination of lipid-regulating drugs may be necessary.

Drug treatment in secondary hypercholesterolaemia If 6–12 months of dietary and other lifestyle interventions has failed to lower cholesterol concentration adequately, drug treatment may be indicated in children 10 years and older (rarely necessary in younger children) who are at a high risk of developing cardiovascular disease.

Choice of drugs Experience in the use of lipid-regulating drugs in children is limited and they should be initiated on specialist advice.

Statins are the drugs of first choice in children and are generally well tolerated; atorvastatin and simvastatin are the preferred statins. Other lipid-regulating drugs can be used if statins are ineffective or are not tolerated.

Ezetimibe can be used alone when statins are not tolerated, or in combination with a statin when a high-dose statin fails to control cholesterol concentration adequately.

Bile acid sequestrants are also available but tolerability of and compliance with these drugs is poor, and their use is declining.

Evidence for the use of a **fibrate** (**bezafibrate** or **feno-fibrate**) in children is limited; fibrates should be considered only if dietary intervention and treatment with a statin and a bile acid sequestrant is unsuccessful or contra-indicated.

In hypertriglyceridaemia which cannot be controlled by very strict diet, omega-3 fatty acid compounds can be considered.

Statins

The statins (**atorvastatin**, **fluvastatin**, **pravastatin**, **rosuvastatin** and **simvastatin**) competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver. They are more effective than other classes of drugs in lowering LDL-cholesterol but less effective than the fibrates in reducing triglycerides. Statins also increase concentrations of HDL-cholesterol.

Statins reduce cardiovascular disease events and total mortality in adults, irrespective of the initial cholesterol concentration.

Cautions Hypothyroidism should be managed adequately before starting treatment with a statin (see Hypothyroidism, above). Statins should be used with caution in those with a history of liver disease or with a high alcohol intake—see also Hepatic Impairment, below. There is little information available on a rational approach to liver-function monitoring; however, a NICE guideline¹ suggests that liver enzymes should be measured before treatment, and repeated within 3 months and at 12 months of starting treatment, unless indicated at other times by signs or symptoms suggestive of hepatotoxicity. Those with serum transaminases that are raised, but less than 3 times the upper limit of the reference range, should **not** be routinely excluded from statin therapy. Those with serum transaminases of more than 3 times the upper limit of the reference range should discontinue statin therapy. Statins should be used with caution in those with risk factors for myopathy or rhabdomyolysis; children or their carers should be advised to report unexplained muscle pain (see Muscle Effects below). Creatine kinase concentration should be measured in children before treatment and if unexplained muscle pain occurs. **Interactions:** Appendix 1 (statins).

Hepatic impairment Statins should be used with caution in those with a history of liver disease and avoided in active liver disease or when there are unexplained persistent elevations in serum transaminases.

Pregnancy Statins should be avoided in pregnancy as congenital anomalies have been reported and the decreased synthesis of cholesterol possibly affects fetal development. Adequate contraception is required during treatment and for 1 month afterwards.

Breast-feeding The manufacturers of atorvastatin, fluvastatin, rosuvastatin, and simvastatin advise avoiding use in mothers who are breast-feeding as there is no information available. The manufacturers of pravastatin advise against use in breast-feeding mothers as a small amount of drug is present in breast milk.

1. NICE clinical guideline 67 (May 2008). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Side-effects The statins have been associated with myalgia, myopathy, myositis, and rhabdomyolysis (see Muscle Effects below). Statins can alter liver function tests, and rarely cause hepatitis and jaundice; pancreatitis and hepatic failure have been reported very rarely. Other side-effects include gastro-intestinal disturbances, sleep disturbance, headache, dizziness, depression, paraesthesia, asthenia, peripheral neuropathy, amnesia, fatigue, sexual dysfunction, thrombocytopenia, arthralgia, visual disturbance, alopecia, and hypersensitivity reactions (including rash, pruritus, urticaria, and very rarely lupus erythematosus-like reactions). In very rare cases, statins can cause interstitial lung disease; if children develop symptoms such as dyspnoea, cough, and weight loss, they should seek medical attention. Statins can cause hyperglycaemia and may be associated with the development of diabetes mellitus, particularly in those already at risk of the condition.

Muscle effects The risk of myopathy, myositis, and rhabdomyolysis associated with statin use is rare. Although myalgia has been reported commonly in those receiving statins, muscle toxicity truly attributable to statin use is rare. Muscle toxicity can occur with all statins, however the likelihood increases with higher doses and in certain individuals (see below). Statins should be used with caution in children at increased risk of muscle toxicity, including those with a personal or family history of muscular disorders, previous history of muscular toxicity, a high alcohol intake, renal impairment, or hypothyroidism. There is an increased incidence of myopathy if a statin is given at a high dose, or if it is given with a fibrate (the combination of a statin and gemfibrozil should preferably be avoided), with lipid-lowering doses of nicotinic acid, with fusidic acid (risk of rhabdomyolysis—the combination of a statin and fusidic acid should be avoided; temporarily discontinue statin and restart 7 days after last fusidic acid dose), or with drugs that increase the plasma-statin concentration, such as macrolide antibiotics, imidazole and triazole antifungals, and ciclosporin—see **Interactions**: Appendix 1 (statins); close monitoring of liver function and, if muscular symptoms occur, of creatine kinase is necessary. In children at increased risk of muscle effects, a statin should not usually be started if the baseline creatine kinase concentration is more than 5 times the upper limit of normal (some children may present with an extremely elevated baseline creatine kinase concentration, due to e.g. rigorous exercise—specialist advice should be sought regarding consideration of statin therapy in these children).

If muscular symptoms or raised creatine kinase occur during treatment, other possible causes (e.g. rigorous physical activity, hypothyroidism, infection, recent trauma, and drug or alcohol addiction) should be excluded before statin therapy is implicated. When a statin is suspected to be the cause of myopathy, and creatine kinase concentration is markedly elevated (more than 5 times upper limit of normal), or if muscular symptoms are severe, treatment should be discontinued. If symptoms resolve and creatine kinase concentrations return to normal, the statin should be reintroduced at a lower dose and the child monitored closely; an alternative statin should be prescribed if unacceptable side-effects are experienced with a particular statin. Statins should not be discontinued in the event of small, asymptomatic elevations of creatine kinase. Routine monitoring of creatine kinase is unnecessary in asymptomatic children.

Counselling Advise children or their carers to report promptly unexplained muscle pain, tenderness, or weakness.

ATORVASTATIN

Cautions see notes above; also haemorrhagic stroke

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also nasopharyngitis, epistaxis, pharyngeolaryngeal pain, back pain,

hyperglycaemia; *less commonly* blurred vision, pyrexia, anorexia, malaise, chest pain, weight gain, hypoglycaemia, tinnitus, peripheral oedema, neck pain; *rarely* cholestasis, Stevens-Johnson syndrome, toxic epidermal necrolysis; *very rarely* gynaecomastia, hearing loss

Indications and dose

Hyperlipidaemia including familial hypercholesterolaemia

• By mouth

Child 10–18 years initially 10 mg once daily, increased if necessary at intervals of at least 4 weeks to usual max. 20 mg once daily (max. 80 mg once daily in homozygous familial hypercholesterolaemia)

Note Reduced dose required (max. 10 mg daily) with concomitant ciclosporin, or tipranavir combined with ritonavir—seek specialist advice (see also Appendix 1)

Atorvastatin (Non-proprietary) (PoM)

Tablets, atorvastatin (as calcium trihydrate) 10 mg, net price 28-tab pack = £1.03; 20 mg, 28-tab pack = £1.26; 40 mg, 28-tab pack = £1.51; 80 mg, 28-tab pack = £2.48. Counselling, muscle effects, see notes above

Lipitor® (Pfizer) (PoM)

Chewable tablets ▼, atorvastatin (as calcium trihydrate) 10 mg, net price 30-tab pack = £13.80; 20 mg, 30-tab pack = £26.40. Label: 24, counselling, muscle effects, see notes above

Tablets, all f/c, atorvastatin (as calcium trihydrate) 10 mg, net price 28-tab pack = £13.00; 20 mg, 28-tab pack = £24.64; 40 mg, 28-tab pack = £24.64; 80 mg, 28-tab pack = £28.21. Counselling, muscle effects, see notes above

FLUVASTATIN

Cautions see notes above

Hepatic impairment see notes above

Renal impairment manufacturer advises doses above 40 mg daily should be initiated with caution if estimated glomerular filtration rate is less than 30 mL/minute/1.73 m²

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also *very rarely* vasculitis

Indications and dose

Heterozygous familial hypercholesterolaemia

• By mouth

Child 9–18 years initially 20 mg daily in the evening, adjusted in steps of 20 mg daily at intervals of at least 6 weeks; max. 80 mg daily (40 mg twice daily)

Fluvastatin (Non-proprietary) (PoM)

Capsules, fluvastatin (as sodium salt) 20 mg, net price 28-cap pack = £2.27; 40 mg, 28-cap pack = £2.37. Counselling, muscle effects, see notes above

Lescol® (Novartis) (PoM)

Capsules, fluvastatin (as sodium salt) 20 mg (brown/yellow), net price 28-cap pack = £15.26; 40 mg (brown/orange), 28-cap pack = £15.26, 56-cap pack = £30.53. Counselling, muscle effects, see notes above

Modified release

Fluvastatin (Non-proprietary) (PoM)

Tablets, m/r, fluvastatin (as sodium salt) 80 mg, net price 28-tab pack = £19.20. Label: 25, counselling, muscle effects, see notes above

Brands include Dorisin[®] XL, Luvinsta[®] XL, Pimactil[®], Steflavin[®] XL

Dose

Child 9–18 years 80 mg once daily (dose form not appropriate for initial dose titration)

Lescol[®] XL (Novartis) (PoM)

Tablets, m/r, yellow, fluvastatin (as sodium salt) 80 mg, net price 28-tab pack = £19.20. Label: 25, counselling, muscle effects, see notes above

Dose

Child 9–18 years 80 mg once daily (dose form not appropriate for initial dose titration)

PRAVASTATIN SODIUM

Cautions see notes above

Hepatic impairment see notes above

Renal impairment start with lower doses in moderate to severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; *less commonly* abnormal urination (including dysuria, nocturia, and frequency); *very rarely* fulminant hepatic necrosis

Indications and dose

Hyperlipidaemia including familial hypercholesterolaemia

• By mouth

Child 8–14 years 10 mg once daily at night, adjusted at intervals of at least 4 weeks to max. 20 mg once daily at night

Child 14–18 years 10 mg once daily at night, adjusted at intervals of at least 4 weeks to max. 40 mg once daily at night

Pravastatin (Non-proprietary) (PoM)

Tablets, pravastatin sodium 10 mg, net price 28-tab pack = £1.16; 20 mg, 28-tab pack = £1.41; 40 mg, 28-tab pack = £1.77. Counselling, muscle effects, see notes above

Lipostat[®] (Squibb) (PoM)

Tablets, all yellow, pravastatin sodium 10 mg, net price 28-tab pack = £14.18; 20 mg, 28-tab pack = £26.01; 40 mg, 28-tab pack = £26.01. Counselling, muscle effects, see notes above

ROSUVASTATIN

Cautions see notes above; children of Asian origin; use lower max. dose in children with risk factors for myopathy or rhabdomyolysis (including personal or family history of muscular disorders or toxicity)

Hepatic impairment see notes above

Renal impairment reduce dose if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also proteinuria; *very rarely* gynaecomastia, haematuria; *also reported* oedema, Stevens-Johnson syndrome

Indications and dose

Hyperlipidaemia including familial hypercholesterolaemia

• By mouth

Child 10–18 years initially 5 mg daily, increased if necessary at intervals of at least 4 weeks to usual max. 20 mg once daily

Note Reduced dose required with concomitant atazanavir, darunavir, ezetimibe, fibrates, itraconazole, lopinavir, or tipranavir—seek specialist advice

Crestor[®] (AstraZeneca) (PoM)

Tablets, f/c, rosuvastatin (as calcium salt) 5 mg (yellow), net price 28-tab pack = £18.03; 10 mg (pink), 28-tab pack = £18.03; 20 mg (pink), 28-tab pack = £26.02. Counselling, muscle effects, see notes above

SIMVASTATIN

Cautions see notes above

Hepatic impairment see notes above

Renal impairment doses above 10 mg daily should be used with caution if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also *rarely* anaemia; *also reported* tendinopathy

Licensed use not licensed for use in children under 10 years

Indications and dose

Hyperlipidaemia including familial hypercholesterolaemia

• By mouth

Child 5–10 years initially 10 mg at night increased, if necessary, at intervals of at least 4 weeks to max. 20 mg at night

Child 10–18 years initially 10 mg at night increased, if necessary, at intervals of at least 4 weeks to max. 40 mg at night

Note Reduced dose required with concomitant amiodarone, bezafibrate, amlodipine, diltiazem, or verapamil—seek specialist advice

Simvastatin (Non-proprietary) ▼ (PoM)

Tablets, simvastatin 10 mg, net price 28-tab pack = 80p; 20 mg, 28-tab pack = 86p; 40 mg, 28-tab pack = £1.09; 80 mg, 28-tab pack = £1.65. Counselling, muscle effects, see notes above

Brands include Simvador[®]

Oral suspension, simvastatin 20 mg/5 mL, net price 150-mL = £111.44, 40 mg/5 mL, 150-mL = £170.24. Counselling, muscle effects, see notes above

Excipients may include propylene glycol

Zocor[®] (MSD) ▼ (PoM)

Tablets, all f/c, simvastatin 10 mg (peach), net price 28-tab pack = £18.03; 20 mg (tan), 28-tab pack = £29.69; 40 mg (red), 28-tab pack = £29.69; 80 mg (red), 28-tab pack = £29.69. Counselling, muscle effects, see notes above

■ With ezetimibe

Note For homozygous familial hypercholesterolaemia, primary hypercholesterolaemia, and mixed hyperlipidaemia in children over 10 years stabilised on the individual components in the same proportions, or for children not adequately controlled by statin alone. Treatment should be initiated by a specialist. For prescribing information on ezetimibe, see Ezetimibe

Inegy® (MSD) (PoM)

Tablets, simvastatin 20 mg, ezetimibe 10 mg, net price 28-tab pack = £33.42; simvastatin 40 mg, ezetimibe 10 mg, 28-tab pack = £38.98; simvastatin 80 mg, ezetimibe 10 mg, 28-tab pack = £41.21. Counselling, muscle effects, see notes above

Bile acid sequestrants

Colestyramine (cholestyramine) and **colestipol** are bile acid sequestrants used in the management of hypercholesterolaemia. They act by binding bile acids, preventing their reabsorption; this promotes hepatic conversion of cholesterol into bile acids; the resultant increased LDL-receptor activity of liver cells increases the clearance of LDL-cholesterol from the plasma. Thus both compounds effectively reduce LDL-cholesterol but can aggravate hypertriglyceridaemia. Bile acid sequestrants are not well tolerated and compliance with treatment is poor, therefore they are rarely used in children.

Cautions Bile acid sequestrants interfere with the absorption of fat-soluble vitamins; supplements of vitamins A, D, K, and folic acid may be required when treatment is prolonged and the child's growth and development should be monitored. **Interactions:** Appendix 1 (bile acid sequestrants).

Pregnancy and breast-feeding Bile acid sequestrants should be used with caution as although the drugs are not absorbed, they may cause fat-soluble vitamin deficiency on prolonged use.

Side-effects As bile acid sequestrants are not absorbed, gastro-intestinal side-effects predominate. Constipation is common, but diarrhoea has occurred, as have nausea, vomiting, and gastro-intestinal discomfort. Hypertriglyceridaemia may be aggravated. An increased bleeding tendency has been reported due to hypoprothrombinaemia associated with vitamin K deficiency.

Counselling Other drugs should be taken at least 1 hour before or 4–6 hours after bile acid sequestrants to reduce possible interference with absorption.

COLESTYRAMINE
(Cholestyramine)

Cautions see notes above

Contra-indications complete biliary obstruction (not likely to be effective)

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; intestinal obstruction reported rarely and hyperchloraemic acidosis reported on prolonged use

Licensed use licensed in children over 6 years to reduce cholesterol; see also section 1.9.2

Indications and dose**Familial hypercholesterolaemia**

- By mouth

Child 6–12 years initially 4 g once daily increased to 4 g up to 3 times daily according to response

Child 12–18 years initially 4 g once daily increased by 4 g at weekly intervals to 12–24 g daily in 1–4 divided doses, then adjusted according to response; max. 36 g daily

Cholestatic pruritus section 1.9.2

Diarrhoea section 1.9.2

Administration The contents of each sachet should be mixed with at least 150 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, and pulpy fruits with a high moisture content; total daily dose may be given as a single dose if tolerated

Colestyramine (Non-proprietary) (PoM)

Powder, sugar-free, colestyramine (anhydrous) 4 g/sachet, net price 50-sachet pack = £29.43. Label: 13, counselling, avoid other drugs at same time (see notes above)

Excipients may include aspartame (section 9.4.1)

Questran® (Bristol-Myers Squibb) (PoM)

Powder, colestyramine (anhydrous) 4 g/sachet, net price 50-sachet pack = £10.76. Label: 13, counselling, avoid other drugs at same time (see notes above)

Excipients include sucrose 3.79 g/sachet

Questran Light® (Bristol-Myers Squibb) (PoM)

Powder, sugar-free, colestyramine (anhydrous) 4 g/sachet, net price 50-sachet pack = £16.15. Label: 13, counselling, avoid other drugs at same time (see notes above)

Excipients include aspartame (section 9.4.1)

COLESTIPOL HYDROCHLORIDE

Cautions see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use not licensed for use in children

Indications and dose**Familial hypercholesterolaemia**

- By mouth

Child 12–18 years initially 5 g 1–2 times daily increased if necessary in 5-g increments at intervals of 1 month to max. of 30 g daily in 1–2 divided doses

Administration the contents of each sachet should be mixed with at least 100 mL of water or other suitable liquid such as fruit juice or skimmed milk; alternatively it can be mixed with thin soups, cereals, yoghurt, or pulpy fruits ensuring at least 100 mL of liquid is provided; total daily dose may be given as a single dose if tolerated

Colestid® (Pharmacia) (PoM)

Granules, yellow, colestipol hydrochloride 5 g/sachet, net price 30 sachets = £15.05. Label: 13, counselling, avoid other drugs at same time (see notes above)

Colestid Orange, granules, yellow/orange, colestipol hydrochloride 5 g/sachet, with aspartame, net price 30 sachets = £15.05. Label: 13, counselling, avoid other drugs at same time (see notes above)

Ezetimibe

Ezetimibe inhibits the intestinal absorption of cholesterol. It is given in combination with a statin or alone if a statin is inappropriate. If ezetimibe is used in combination with a statin, there is an increased risk of rhabdomyolysis (see also Muscle Effects, p. 125)

EZETIMIBE

Cautions interactions: Appendix 1 (ezetimibe)

Hepatic impairment avoid in moderate and severe impairment—may accumulate

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—present in milk in animal studies

Side-effects gastro-intestinal disturbances; headache, fatigue; myalgia; *rarely* arthralgia, hypersensitivity reactions (including rash, angioedema, and anaphylaxis), hepatitis; *very rarely* pancreatitis, cholelithiasis, cholecystitis, thrombocytopenia, raised creatine kinase, myopathy, and rhabdomyolysis

Indications and dose

Adjunct to dietary measures and statin treatment in primary hypercholesterolaemia and homozygous familial hypercholesterolaemia (ezetimibe alone in primary hypercholesterolaemia if statin inappropriate or not tolerated); adjunct to dietary measures in homozygous sitosterolaemia

• By mouth

Child 10–18 years 10 mg once daily

Ezetrol® (MSD) (PoM)

Tablets, ezetimibe 10 mg, net price 28-tab pack = £26.31

With simvastatin

See under Simvastatin

Fibrates

Bezafibrate and **fenofibrate** act mainly by decreasing serum triglycerides; they have variable effects on LDL-cholesterol. Fibrates may reduce the risk of coronary heart disease in those with low HDL-cholesterol or with raised triglycerides.

Fibrates can cause a myositis-like syndrome, especially in children with impaired renal function. Also, combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution (see Muscle Effects, p. 125).

There is limited evidence to support their use in children and they should only be considered if treatment with a statin and a bile acid sequestrant is unsuccessful or contra-indicated.

BEZAFIBRATE

Cautions correct hypothyroidism before initiating treatment (see Hypothyroidism, p. 124); **interactions:** Appendix 1 (fibrates)

Contra-indications hypoalbuminaemia; gall bladder disease; nephrotic syndrome; photosensitivity to fibrates

Hepatic impairment avoid in severe liver disease

Renal impairment reduce dose if estimated glomerular filtration rate 15–60 mL/minute/1.73 m²; avoid

if estimated glomerular filtration rate less than 15 mL/minute/1.73 m²

Myotoxicity Special care needed in children with renal disease, as progressive increases in serum-creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly

Pregnancy manufacturers advise avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects abdominal distension, diarrhoea, nausea, anorexia; *less commonly* cholestasis, dizziness, headache, renal failure, erectile dysfunction, myotoxicity (with myasthenia, myalgia, or very rarely rhabdomyolysis)—particular risk in renal impairment (see Myotoxicity above), urticaria, pruritus, rash, photosensitivity reactions, alopecia; *rarely* pancreatitis, peripheral neuropathy; *very rarely* gallstones, interstitial lung disease, anaemia, leucopenia, pancytopenia, increased platelet count, thrombocytopenic purpura, Stevens-Johnson syndrome, toxic epidermal necrolysis

Licensed use not licensed for use in children

Indications and dose

Hyperlipidaemia including familial hypercholesterolaemia (on specialist advice only)

• By mouth

Child 10–18 years 200 mg once daily adjusted according to response to max. 200 mg 3 times daily

Bezafibrate (Non-proprietary) (PoM)

Tablets, bezafibrate 200 mg, net price 100-tab pack = £5.15. Label: 21

Bezalip® (Actavis) (PoM)

Tablets, f/c, bezafibrate 200 mg, net price 100-tab pack = £8.63. Label: 21

FENOFIBRATE

Cautions see under Bezafibrate; liver function tests recommended every 3 months for first year (discontinue treatment if significantly raised)

Contra-indications gall bladder disease; pancreatitis (unless due to severe hypertriglyceridaemia); photosensitivity to ketoprofen

Hepatic impairment avoid

Renal impairment reduce dose if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 15 mL/minute/1.73 m²

Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum-creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly

Pregnancy avoid—embryotoxicity in animal studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects see under Bezafibrate; also *less commonly* pancreatitis, pulmonary embolism; *rarely* hepatitis; *also reported* interstitial pneumopathies

Indications and dose

See under preparations

Fenofibrate (Non-proprietary) (PoM)

Capsules, fenofibrate (micronised) 67 mg, net price 90-cap pack = £18.31. Label: 21

Dose

Hyperlipidaemias including familial hypercholesterolaemia (on specialist advice only)

• By mouth

Child 4–15 years 1 capsule/20 kg body-weight (max. 4 capsules or max. 3 capsules with concomitant statin) daily

Child 15–18 years initially 3 capsules daily, increased if necessary to 4 capsules daily (max. 3 capsules daily with concomitant statin)

Lipantil[®] (Abbott Healthcare) (PoM)

Lipantil[®] Micro 67 capsules, yellow, fenofibrate (micronised) 67 mg, net price 90-cap pack = £23.30. Label: 21

Dose

Hyperlipidaemias including familial hypercholesterolaemia (on specialist advice only)

• By mouth

Child 4–15 years 1 capsule/20 kg body-weight (max. 4 capsules or max. 3 capsules with concomitant statin) daily

Child 15–18 years initially 3 capsules daily, increased if necessary to 4 capsules daily (max. 3 capsules daily with concomitant statin)

2.13 Local sclerosants

Classification not used in *BNF for Children*.

2.14 Drugs affecting the ductus arteriosus

Closure of the ductus arteriosus

Patent ductus arteriosus is a frequent problem in premature neonates with respiratory distress syndrome. Substantial left-to-right shunting through the ductus arteriosus may increase the risk of intraventricular haemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia, and possibly death.

Indometacin or ibuprofen can be used to close the ductus arteriosus. **Indometacin** has been used for many years and is effective but it reduces cerebral blood flow, and causes a transient fall in renal and gastro-intestinal blood flow. **Ibuprofen** may also be used; it has little effect on renal function (there may be a small reduction in sodium excretion) when used in doses for closure of the ductus arteriosus; gastro-intestinal problems are uncommon.

If drug treatment fails to close the ductus arteriosus, surgery may be indicated.

IBUPROFEN

Cautions may mask symptoms of infection; monitor for bleeding; monitor gastro-intestinal function; allergic disorders; **interactions**: Appendix 1 (NSAIDs)

Contra-indications life-threatening infection; active bleeding especially intracranial or gastro-intestinal; thrombocytopenia or coagulation defects; marked unconjugated hyperbilirubinaemia; known or sus-

pected necrotising enterocolitis; pulmonary hypertension

Hepatic impairment increased risk of gastro-intestinal bleeding and fluid retention; avoid in severe liver disease

Renal impairment use lowest effective dose and monitor renal function; sodium and water retention; deterioration in renal function possibly leading to renal failure; avoid if possible in severe impairment

Side-effects intestinal perforation; intraventricular haemorrhage; ischaemic brain injury; bronchopulmonary dysplasia, pulmonary haemorrhage; thrombocytopenia, neutropenia, oliguria, haematuria, fluid retention, hyponatraemia; *less commonly* gastro-intestinal haemorrhage; hypoxaemia

Licensed use Orphan licence for the injection for closure of ductus arteriosus in premature neonates less than 34 weeks corrected gestational age

Indications and dose

Closure of ductus arteriosus

• By slow intravenous injection

Neonate initially 10 mg/kg as a single dose followed at 24-hour intervals by 2 doses of 5 mg/kg; course may be repeated after 48 hours if necessary

Mild to moderate pain, pain and inflammation of soft tissue injuries and rheumatic disease, pyrexia section 10.1.1

Administration for *slow intravenous injection*, give over 15 minutes, preferably undiluted. May be diluted with Glucose 5% or Sodium Chloride 0.9%

Pedea[®] (Orphan Europe) (PoM)

Intravenous solution, ibuprofen 5 mg/mL, net price 4 × 2-mL vials = £288.00

INDOMETACIN

Cautions see notes above; also may mask symptoms of infection; may reduce urine output by 50% or more (monitor carefully—see also under Anuria or Oliguria, below) and precipitate renal impairment especially if extracellular volume depleted, heart failure, sepsis, or concomitant use of nephrotoxic drugs; may induce hyponatraemia; inhibition of platelet aggregation (monitor for bleeding); **interactions**: Appendix 1 (NSAIDs)

Contra-indications untreated infection, bleeding (especially with active intracranial haemorrhage or gastro-intestinal bleeding); thrombocytopenia, coagulation defects, necrotising enterocolitis

Hepatic impairment increased risk of gastro-intestinal bleeding and fluid retention; avoid in severe impairment

Renal impairment use lowest effective dose and monitor renal function; sodium and water retention; deterioration in renal function possibly leading to renal failure; avoid if possible in severe impairment

Anuria or oliguria If anuria or marked oliguria (urinary output less than 0.6 mL/kg/hour), delay further doses until renal function returns to normal

Side-effects haemorrhagic, renal, gastro-intestinal, metabolic, and coagulation disorders; pulmonary hypertension, intracranial bleeding, fluid retention, and exacerbation of infection

Indications and dose**Symptomatic ductus arteriosus**

- By intravenous infusion over 20–30 minutes

Neonate initially 100–200 micrograms/kg as a single dose followed by 2 doses of 100 micrograms/kg at 24-hour intervals; if residual patency present, give 100 micrograms/kg for a further 3 doses at 24-hour intervals

Note Monitor carefully to ensure adequate urine output, see Anuria or Oliguria above

Pain and inflammation in rheumatic disease section 10.1.1

Administration for intravenous infusion, dilute each vial with 1–2 mL Sodium Chloride 0.9% or Water for Injections

Indometacin (Non-proprietary) (PoM)

Injection, indometacin

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Maintenance of patency

In the newborn with duct-dependent congenital heart disease it is often necessary to maintain the patency of the ductus arteriosus whilst awaiting surgery.

Alprostadil (prostaglandin E1) and **dinoprostone** (prostaglandin E2) are potent vasodilators that are effective for maintaining the patency of the ductus arteriosus. They are usually given by continuous intravenous infusion, but oral dosing of dinoprostone is still used in some centres.

During the infusion of a prostaglandin, the newborn requires careful monitoring of heart rate, blood pressure, respiratory rate, and core body temperature. In the event of complications such as apnoea, profound bradycardia, or severe hypotension, the infusion should be temporarily stopped and the complication dealt with; the infusion should be restarted at a lower dose. Recurrent or prolonged apnoea may require ventilatory support in order for the prostaglandin infusion to continue.

ALPROSTADIL

Cautions see notes above; also history of haemorrhage; avoid in hyaline membrane disease; monitor arterial pressure, respiratory rate, heart rate, temperature, and venous blood pressure in arm and leg; facilities for intubation and ventilation must be immediately available; **interactions:** Appendix 1 (alprostadil)

Side-effects apnoea (particularly in neonates under 2 kg), flushing, bradycardia, hypotension, tachycardia, cardiac arrest, oedema, diarrhoea, fever, convulsions, disseminated intravascular coagulation, hypokalaemia; cortical proliferation of long bones; weakening of the wall of the ductus arteriosus and pulmonary artery may follow prolonged use; gastric-outlet obstruction reported

Indications and dose**Maintaining patency of the ductus arteriosus**

- By continuous intravenous infusion

Neonate initially 5 nanograms/kg/minute, adjusted according to response in steps of 5 nanograms/kg/minute; max. 100 nanograms/kg/minute (but associated with increased side-effects)

Note Alprostadil doses in BNFC may differ from those in product literature

Administration dilute 150 micrograms/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 nanograms/kg/minute. Undiluted solution must not come into contact with the barrel of the plastic syringe; add the required volume of alprostadil to a volume of infusion fluid in the syringe and then make up to final volume

Prostin VR[®] (Pharmacia) (PoM)

Intravenous solution, alprostadil 500 micrograms/mL in alcohol. For dilution and use as an infusion. Net price 1-mL amp = £75.19 (hosp.only)

DINOPROSTONE

Cautions see notes above; also history of haemorrhage; avoid in hyaline membrane disease; monitor arterial oxygenation, heart rate, temperature, and blood pressure in arm and leg; facilities for intubation and ventilation must be immediately available; **interactions:** Appendix 1 (prostaglandins)

Hepatic impairment manufacturer advises avoid

Renal impairment manufacturer advises avoid

Side-effects nausea, vomiting, diarrhoea; flushing, bradycardia, hypotension, cardiac arrest; respiratory depression and apnoea, particularly with high doses and in low birth-weight neonates, bronchospasm; pyrexia and raised white blood cell count, shivering; local reactions, erythema; if used for longer than 5 days, gastric outlet obstruction; cortical hyperostosis (prolonged use)

Licensed use not licensed for use in children

Indications and dose**Maintaining patency of the ductus arteriosus**

- By continuous intravenous infusion

Neonate initially 5 nanograms/kg/minute, increased as necessary in 5 nanogram/kg/minute increments to 20 nanograms/kg/minute

Note Doses up to 100 nanograms/kg/minute have been used but are associated with increased side-effects

- By mouth

Neonate 20–25 micrograms/kg every 1–2 hours doubled if necessary; if treatment continues for more than 1 week gradually reduce the dose

Administration for continuous intravenous infusion, dilute to a concentration of 1 microgram/mL with Glucose 5% or Sodium Chloride 0.9%.

For administration by mouth, injection solution can be given orally; dilute with water

Prostin[®] E2 (Pharmacia) (PoM)

Intravenous solution, for dilution and use as an infusion, dinoprostone 1 mg/mL, net price 0.75-mL amp = £8.52; 10 mg/mL, 0.5-mL amp = £18.40 (both hosp. only)

3 Respiratory system

3.1	Bronchodilators	131
3.1.1	Adrenoceptor agonists	135
3.1.1.1	Selective beta₂ agonists	135
3.1.1.2	Other adrenoceptor agonists	139
3.1.2	Antimuscarinic bronchodilators	139
3.1.3	Theophylline	140
3.1.4	Compound bronchodilator preparations	142
3.1.5	Peak flow meters, inhaler devices, and nebulisers	142
3.2	Corticosteroids	144
3.3	Cromoglicate and related therapy and leukotriene receptor antagonists	150
3.3.1	Cromoglicate and related therapy	150
3.3.2	Leukotriene receptor antagonists	150
3.4	Antihistamines, immunotherapy, and allergic emergencies	151
3.4.1	Antihistamines	151
3.4.2	Allergen immunotherapy	156
3.4.3	Allergic emergencies	158
3.5	Respiratory stimulants and pulmonary surfactants	161
3.5.1	Respiratory stimulants	161
3.5.2	Pulmonary surfactants	162
3.6	Oxygen	162
3.7	Mucolytics	164
3.8	Aromatic inhalations	166
3.9	Cough preparations	166
3.9.1	Cough suppressants	166
3.9.2	Expectorant and demulcent cough preparations	167
3.10	Systemic nasal decongestants	167
3.11	Antifibrotics	167

This chapter includes advice on the drug management of the following:

acute asthma, p. 132
 anaphylaxis, p. 158
 angioedema, p. 160
 chronic asthma, p. 133
 croup, p. 135

3.1 Bronchodilators

3.1.1	Adrenoceptor agonists
3.1.2	Antimuscarinic bronchodilators
3.1.3	Theophylline
3.1.4	Compound bronchodilator preparations
3.1.5	Peak flow meters, inhaler devices, and nebulisers

Asthma

Drugs used in the management of asthma include beta₂ agonists (section 3.1.1), antimuscarinic bronchodilators (section 3.1.2), theophylline (section 3.1.3), corticosteroids (section 3.2), cromoglicate and nedocromil (section 3.3.1), leukotriene receptor antagonists (section 3.3.2), and in specialist centres, omalizumab (section 3.4.2).

For tables outlining the management of chronic asthma and management of acute asthma, see p. 133 and p. 134.

Administration of drugs for asthma

Inhalation This route delivers the drug directly to the airways; the dose required is smaller than when given by mouth and side-effects are reduced. See Inhaler devices, section 3.1.5.

Solutions for nebulisation for use in acute severe asthma are administered over 5–10 minutes from a nebuliser, usually driven by oxygen in hospital. See Nebulisers, section 3.1.5.

Oral Systemic side-effects occur more frequently when a drug is given orally rather than by inhalation. Oral corticosteroids, theophylline, and leukotriene receptor antagonists are sometimes required for the management of asthma. Oral administration of a beta₂ agonist is generally not recommended for children, but may be necessary in infants and young children who are unable or unwilling to use an inhaler device.

Parenteral Drugs such as beta₂ agonists, corticosteroids, and aminophylline can be given by injection in acute severe asthma when drug administration by nebulisation is inadequate or inappropriate; in these circumstances the child should generally be treated in a high-dependency or intensive care unit.

Pregnancy and breast-feeding

Women with asthma should be closely monitored during pregnancy. Well-controlled asthma has no important effects on pregnancy, labour, or the fetus. Drugs for

asthma should preferably be administered by inhalation to minimise fetal drug exposure. Inhaled drugs, theophylline, and prednisolone can be taken as normal during pregnancy and breast-feeding. For the use of leukotriene receptor antagonists during pregnancy see section 3.3.2. Women planning to become pregnant should be counselled about the importance of taking their asthma medication regularly to maintain good control.

Severe acute exacerbations of asthma can have an adverse effect on pregnancy and should be treated promptly in hospital with conventional therapy, including nebulisation of a β_2 agonist, and oral or parenteral administration of a corticosteroid; prednisolone is the preferred corticosteroid for oral administration since very little of the drug reaches the fetus. Oxygen should be given immediately to maintain an arterial oxygen saturation of 94–98% and prevent maternal and fetal hypoxia. An intravenous β_2 agonist, aminophylline, or magnesium sulfate can be used during pregnancy if necessary; parenteral β_2 agonists can affect the myometrium, see BNF section 7.1.3.

Management of acute asthma¹

Important

Regard each emergency consultation as being for **severe acute asthma** until shown otherwise.

Failure to respond adequately at **any time** requires immediate transfer to hospital.

Severe acute asthma can be fatal and must be treated promptly. Treatment of severe acute asthma is safer in hospital where resuscitation facilities are immediately available. Treatment should **never** be delayed for investigations, children should **never** be sedated, and the possibility of a pneumothorax should be considered. If the child's condition deteriorates despite pharmacological treatment, urgent transfer to a paediatric intensive care unit should be arranged. For a table outlining the management of severe acute asthma, see Management of acute asthma table, p. 134.

Mild to moderate acute asthma Administer a **short-acting β_2 agonist** using a pressurised metered-dose inhaler with a spacer device; for a child under 3 years use a close-fitting facemask. Give 1 puff every 15–30 seconds up to a maximum of 10 puffs; repeat dose after 10–20 minutes if necessary.

Give **prednisolone** by mouth, child under 12 years 1–2 mg/kg (max. 40 mg) once daily for up to 3 days, or longer if necessary; if the child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (max. 60 mg) once daily. For children 12–18 years, give prednisolone 40–50 mg daily for at least 5 days.

If response is poor or if a relapse occurs within 3–4 hours, transfer child **immediately** to hospital for assessment and further treatment.

Children under 18 months often respond poorly to bronchodilators; nebulised β_2 agonists have been associated with mild (but occasionally severe) paradoxical bronchospasm and transient worsening of oxygen saturation; response to prednisolone may also be poor in this age group.

Severe or life-threatening acute asthma Start treatment below and transfer **immediately** to hospital. Administer high-flow **oxygen** (section 3.6) using a close-fitting face mask or nasal prongs.

Treat severe or life-threatening acute exacerbations of asthma with an inhaled **short-acting β_2 agonist** (as above). Treatment of life-threatening asthma should be initiated with nebulised salbutamol 2.5 mg or terbutaline 5 mg (via an oxygen-driven nebuliser if available); nebulised doses may be doubled for children over 5 years. Repeat the dose every 20–30 minutes or as necessary, then reduce the frequency on improvement.

Give **prednisolone** by mouth, child under 12 years 1–2 mg/kg (max. 40 mg) once daily for up to 3 days, or longer if necessary; if the child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (max. 60 mg) once daily. For children 12–18 years, give prednisolone 40–50 mg daily for at least 5 days. If oral administration is not possible, use intravenous **hydrocortisone** (preferably as sodium succinate) 4 mg/kg (max. 100 mg) every 6 hours (alternatively, if weight unavailable, child under 2 years 25 mg every 6 hours, 2–5 years 50 mg every 6 hours, 5–18 years 100 mg every 6 hours).

If response is poor, add nebulised **ipratropium bromide**, child under 12 years give 250 micrograms every 20–30 minutes for the first 2 hours, then every 4–6 hours as necessary. For children 12–18 years, give ipratropium bromide 500 micrograms every 4–6 hours as necessary.

If the condition does not respond or is life-threatening, transfer the child to an intensive care unit and treat with a parenteral **short-acting β_2 agonist** (e.g. salbutamol, section 3.1.1.1) or parenteral **aminophylline** (section 3.1.3). Children over 2 years with severe acute asthma may be helped by intravenous infusion of **magnesium sulfate injection** 40 mg/kg, max. 2 g, (equivalent to approx. 0.16 mmol/kg Mg^{2+} , max. 8 mmol Mg^{2+}) over 20 minutes (section 9.5.1.3), but evidence of benefit is limited.

Follow-up in all cases Episodes of acute asthma should be regarded as a failure of preventive therapy. A careful history should be taken to establish the reason for the exacerbation. Inhaler technique should be checked and regular treatment should be reviewed in accordance with the Management of Chronic Asthma table, p. 133. Children or their carers should be given an asthma action plan aimed at preventing relapse, optimising treatment, and preventing delay in seeking assistance in future exacerbations. If possible, follow-up within 48 hours should be arranged with the general practitioner or appropriate primary care health professional. Children should also be reviewed in a paediatric asthma clinic within 1–2 months of the exacerbation, and referred to a paediatric respiratory specialist if the exacerbation included life-threatening features.

1. Advice on the management of acute asthma is based on the recommendations of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (updated January 2012); updates available at www.brit-thoracic.org.uk

Management of chronic asthma

Important Start at step most appropriate to initial severity; before initiating a new drug consider whether diagnosis is correct, check compliance and inhaler technique, and eliminate trigger factors for acute exacerbations	
Child 5–18 years	Child under 5 years⁴
Step 1: occasional relief bronchodilator Inhaled short-acting beta ₂ agonist as required (up to once daily) Note Move to step 2 if needed more than twice a week, or if night-time symptoms at least once a week, or if exacerbation in the last 2 years	Step 1: occasional relief bronchodilator Short-acting beta ₂ agonist as required (not more than once daily) Note Preferably by inhalation (less effective and more side-effects when given as tablets or syrup) Move to step 2 if needed more than twice a week, or if night-time symptoms at least once a week, or if exacerbation in the last 2 years
Step 2: regular inhaled preventer therapy Inhaled short-acting beta ₂ agonist as required <i>plus</i> Regular standard-dose ¹ inhaled corticosteroid (alternatives ² are considerably less effective)	Step 2: regular preventer therapy Inhaled short-acting beta ₂ agonist as required <i>plus</i> Regular standard-dose ¹ inhaled corticosteroid Or leukotriene receptor antagonist if inhaled corticosteroid cannot be used
Step 3: inhaled corticosteroid + inhaled long-acting beta₂ agonist Inhaled short-acting beta ₂ agonist as required <i>plus</i> Regular standard-dose ¹ inhaled corticosteroid <i>plus</i> Regular inhaled long-acting beta ₂ agonist (salmeterol or formoterol) <i>If asthma not controlled</i> Increase dose of inhaled corticosteroid to upper end of standard dose range ¹ <i>and</i> <i>Either</i> stop long-acting beta ₂ agonist if of no benefit <i>Or</i> continue long-acting beta ₂ agonist if of some benefit <i>If asthma still not controlled and long-acting beta₂ agonist stopped, add one of</i> Leukotriene receptor antagonist Modified-release oral theophylline	Step 3: add-on therapy Child under 2 years: Refer to respiratory paediatrician Child 2–5 years: Inhaled short-acting beta ₂ agonist as required <i>plus</i> Regular standard-dose ¹ inhaled corticosteroid <i>plus</i> Leukotriene receptor antagonist
Step 4: high-dose inhaled corticosteroid + regular bronchodilators Inhaled short-acting beta ₂ agonist as required <i>with</i> Regular high-dose ³ inhaled corticosteroid <i>plus</i> Inhaled long-acting beta ₂ agonist (if of benefit) <i>plus</i> A 6-week sequential therapeutic trial of one or more of Leukotriene receptor antagonist Modified-release oral theophylline Modified-release oral beta ₂ agonist	Step 4: persistent poor control Refer to respiratory paediatrician
Step 5: regular corticosteroid tablets Refer to respiratory paediatrician Inhaled short-acting beta ₂ agonist as required <i>with</i> Regular high-dose ³ inhaled corticosteroid <i>and</i> One or more long-acting bronchodilators (see step 4) <i>plus</i> Regular prednisolone tablets (as single daily dose) Note In addition to regular prednisolone, continue high-dose inhaled corticosteroid (in exceptional cases may exceed licensed doses)	Stepping down Regularly review need for treatment
Stepping down Review treatment every 3 months; if control achieved, step-wise reduction may be possible; reduce dose of inhaled corticosteroid slowly (consider reduction every 3 months, decreasing dose by up to 50% each time) to the lowest dose which controls asthma	1. Standard doses of inhaled corticosteroids Beclometasone dipropionate or budesonide: Child under 12 years 100–200 micrograms twice daily; Child 12–18 years 100–400 micrograms twice daily. Fluticasone propionate: Child 4–12 years 50–100 micrograms twice daily; Child 12–18 years 50–200 micrograms twice daily. Mometasone furoate: Child 12–18 years 400 micrograms as a single dose in the evening or in 2 divided doses. Note Dose adjustments may be required for some inhaler devices, see under individual preparations, section 3.2 2. Alternatives to inhaled corticosteroid are leukotriene receptor antagonists, theophylline, inhaled nedocromil, or inhaled cromoglicic acid 3. High doses of inhaled corticosteroids Beclometasone dipropionate or budesonide: Child 5–12 years 200–400 micrograms twice daily; Child 12–18 years 0.4–1 mg twice daily. Fluticasone propionate: Child 5–12 years 100–200 micrograms twice daily; Child 12–18 years 200–500 micrograms twice daily. Mometasone furoate: Child 12–18 years 400 micrograms twice daily. Note Dose adjustments may be required for some inhaler devices, see under individual preparations, section 3.2. Failure to achieve control with these doses is unusual, see also Side-effects of Inhaled Corticosteroids, section 3.2 4. Lung-function measurements cannot be used to guide management in those under 5 years
Advice on the management of chronic asthma is based on the recommendations of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (updated January 2012); updates available at www.brit-thoracic.org.uk	

Management of acute asthma

Important The assessment of acute asthma in early childhood can be difficult. Children with severe or life-threatening acute asthma may not be distressed and may not have all of these abnormalities; the presence of any should alert the doctor. Regard each emergency consultation as being for **severe acute asthma** until shown otherwise

Moderate acute asthma	Severe acute asthma	Life-threatening acute asthma
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- Able to talk
- Respiration (breaths/minute)
Child 2–5 years ≤ 40 , 5–12 years ≤ 30 , 12–18 years < 25
- Pulse (beats/minute) **Child** 2–5 years ≤ 140 , 5–12 years ≤ 125 , 12–18 years < 110
- Arterial oxygen saturation $\geq 92\%$
- Peak flow **Child** 5–12 years $\geq 50\%$ of predicted or best, 12–18 years $> 50\%$

Treat at home or in surgery and assess response to treatment

- **Child** under 12 years too breathless to talk or feed, 12–18 years cannot complete sentences in one breath
- Use of accessory breathing muscles
- Respiration (breaths/minute)
Child 2–5 years > 40 ; 5–12 years > 30 , 12–18 years ≥ 25
- Pulse (beats/minute) **Child** 2–5 years > 140 ; 5–12 years > 125 , 12–18 years ≥ 110
- Arterial oxygen saturation **Child** under 12 years $< 92\%$, 12–18 years $\geq 92\%$
- Peak flow **Child** 5–12 years $< 50\%$ of predicted or best, 12–18 years 33–50%

Start treatment below and send immediately to hospital

- Silent chest, cyanosis, poor respiratory effort
- Arrhythmia, hypotension
- Exhaustion, altered consciousness, agitation, confusion
- Arterial oxygen saturation $< 92\%$
- Peak flow $< 33\%$ of predicted or best

Start treatment below and send immediately to hospital; consult with senior medical staff and refer to paediatric intensive care

Treatment

- Inhaled short-acting β_2 agonist via a large-volume spacer (and a close-fitting face mask if child under 3 years) or oxygen-driven nebuliser (if available); give 2–10 puffs of **salbutamol** 100 micrograms/metered inhalation each inhaled separately, and repeat at 10–20 minute intervals if necessary or give nebulised **salbutamol**, **Child** under 5 years 2.5 mg, 5–12 years 2.5–5 mg, 12–18 years 5 mg or **terbutaline**, **Child** under 5 years 5 mg, 5–12 years 5–10 mg, 12–18 years 10 mg, and repeat at 20–30 minute intervals as necessary
- **Prednisolone** by mouth **Child** under 12 years 1–2 mg/kg (max. 40 mg) daily for up to 3 days or longer if necessary; if the child has been taking an oral corticosteroid for more than a few days, give **prednisolone** 2 mg/kg (max. 60 mg); **Child** 12–18 years 40–50 mg daily for at least 5 days

Monitor response for 15–30 minutes

If response is poor or a relapse occurs in 3–4 hours, send immediately to hospital for assessment and further treatment

Treatment

- High-flow oxygen (if available)
- Inhaled short-acting β_2 agonist via a large-volume spacer (and a close-fitting face mask if child under 3 years) or oxygen-driven nebuliser (if available) as for moderate acute asthma
- **Prednisolone** by mouth as for moderate acute asthma or intravenous **hydrocortisone** (preferably as sodium succinate) 4 mg/kg (max. 100 mg) every 6 hours (alternatively, if weight unavailable, **Child** under 2 years 25 mg, 2–5 years 50 mg, 5–18 years 100 mg, every 6 hours) until conversion to oral **prednisolone** is possible

Monitor response for 15–30 minutes

If response is poor:

- Inhaled **ipratropium bromide** via oxygen-driven nebuliser (if available), **Child** under 12 years 250 micrograms repeated every 20–30 minutes for the first 2 hours, then every 4–6 hours as necessary; **Child** 12–18 years, 500 micrograms every 4–6 hours as necessary

Refer those who fail to respond and require ventilatory support to a paediatric intensive care or high-dependency unit

- Consider intravenous β_2 agonist, **aminophylline**, or **magnesium sulfate** [unlicensed indication] only after consultation with senior medical staff

Treatment

- High-flow oxygen (if available)
- Inhaled short-acting β_2 agonist via oxygen-driven nebuliser (if available); give **salbutamol**, **Child** under 5 years 2.5 mg, 5–12 years 2.5–5 mg, 12–18 years 5 mg, or **terbutaline**, **Child** under 5 years 5 mg, 5–12 years 5–10 mg, 12–18 years 10 mg, and repeat as necessary; reserve intravenous β_2 agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect
- **Prednisolone** by mouth as for moderate acute asthma or intravenous **hydrocortisone** as for severe acute asthma
- Inhaled **ipratropium bromide** via oxygen-driven nebuliser (if available) as for severe acute asthma

Monitor response for 15–30 minutes

If response is poor:

- Consider intravenous β_2 agonists, **aminophylline**, or **magnesium sulfate** [unlicensed indication] only after consultation with senior medical staff

Follow up in all cases

Monitor symptoms and peak flow. Set up asthma action plan and check inhaler technique with child and carer

Review by general practitioner or appropriate primary care health professional within 48 hours, see also p. 132

Advice on the management of acute asthma is based on the recommendations of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (updated January 2012); updates available at www.brit-thoracic.org.uk

Croup

Mild croup is largely self-limiting, but treatment with a single dose of a corticosteroid (e.g. **dexamethasone** 150 micrograms/kg) by mouth is of benefit.

Severe croup (or mild croup that might cause complications) calls for hospital admission—a single dose of either dexamethasone 150 micrograms/kg or prednisolone 1–2 mg/kg, can be administered by mouth before transfer to hospital. In hospital, dexamethasone 150 micrograms/kg (by mouth or by injection) or budesonide 2 mg by nebulisation (section 3.2) will often reduce symptoms; the dose may be repeated after 12 hours if necessary.

For severe croup not effectively controlled with corticosteroid treatment, nebulised **adrenaline** (section 3.4.3) solution 1 in 1000 (1 mg/mL) can be given with close clinical monitoring in a dose of 400 micrograms/kg (max. 5 mg) repeated after 30 minutes if necessary (the dose may be diluted with sterile sodium chloride 0.9% solution). The effects of nebulised adrenaline last 2–3 hours; the child needs to be carefully monitored for recurrence of the obstruction.

3.1.1 Adrenoceptor agonists (Sympathomimetics)

3.1.1.1 Selective beta₂ agonists

3.1.1.2 Other adrenoceptor agonists

The selective beta₂ agonists (selective beta₂-adrenoceptor agonists, selective beta₂ stimulants) such as salbutamol or terbutaline are the safest and most effective short-acting beta₂ agonists for the treatment of asthma.

Adrenaline (epinephrine), which has both alpha- and beta-adrenoceptor agonist properties, is used in the emergency management of acute allergic and anaphylactic reactions (section 3.4.3); it is also used as a nebuliser solution to treat severe croup.

3.1.1.1 Selective beta₂ agonists

Selective beta₂ agonists produce bronchodilation. A short-acting beta₂ agonist is used for immediate relief of asthma symptoms while a long-acting beta₂ agonist is used in addition to an inhaled corticosteroid in children requiring prophylactic treatment.

Management of Chronic Asthma table, see p. 133
Management of Acute Asthma table, see p. 134
For guidance on the use of inhalers and spacer devices, see section 3.1.5

Short-acting beta₂ agonists Mild to moderate symptoms of asthma respond rapidly to the inhalation of a selective short-acting beta₂ agonist such as **salbutamol** or **terbutaline**. If beta₂ agonist inhalation is needed more often than twice a week, or if night-time symptoms occur at least once a week, or if there has been an exacerbation in the last 2 years, prophylactic treatment should be considered, using a stepped approach as outlined in the Management of Chronic Asthma table, p. 133.

A short-acting beta₂ agonist inhaled immediately before exertion reduces *exercise-induced asthma*; however, frequent exercise-induced asthma probably reflects poor overall control and calls for reassessment of asthma treatment.

Long-acting beta₂ agonists **Formoterol** and **salmeterol** are longer-acting beta₂ agonists which are administered by inhalation. They should be used for asthma only in children who regularly use an inhaled corticosteroid (see CHM advice below). They have a role in the long-term control of chronic asthma (see Management of Chronic Asthma table, p. 133) and they can be useful in nocturnal asthma. Salmeterol should not be used for the relief of an asthma attack; it has a slower onset of action than salbutamol or terbutaline. Formoterol is licensed for short-term symptom relief and for the prevention of exercise-induced bronchospasm; its speed of onset of action is similar to that of salbutamol. **Vilanterol** is a long-acting beta₂ agonist available only in a combination inhaler with fluticasone furoate (see section 3.2).

Combination inhalers that contain a long-acting beta₂ agonist and a corticosteroid (section 3.2) ensure that long-acting beta₂ agonists are not used without concomitant corticosteroids, but reduce the flexibility to adjust the dose of each component.

CHM advice

To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting beta₂ agonists (formoterol and salmeterol) should:

- be added only if regular use of standard-dose inhaled corticosteroids has failed to control asthma adequately;
- not be initiated in patients with rapidly deteriorating asthma;
- be introduced at a low dose and the effect monitored before considering dose increase;
- be discontinued in the absence of benefit;
- not be used for the relief of exercise-induced asthma symptoms unless regular inhaled corticosteroids are also used;
- be reviewed as clinically appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved.

A daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose.

Children and their carers should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta₂ agonist, see Management of Chronic Asthma table, p. 133.

Inhalation A *pressurised metered-dose inhaler* is an effective method of drug administration in mild to moderate chronic asthma; to deliver the drug effectively particularly in children under 12 years, a spacer device should be used (see also NICE guidance, section 3.1.5). When a pressurised metered-dose inhaler with a spacer is unsuitable or inconvenient, a *dry-powder inhaler* or *breath-actuated inhaler* may be used instead if the child is able to use the device effectively. At recommended inhaled doses the duration of action of salbutamol and terbutaline is about 3 to 5 hours and for salmeterol and formoterol is about 12 hours. The **dose**, the frequency, and the maximum number of inhalations in 24 hours of the beta₂ agonist should be **stated explicitly** to the child

and the child's carer. High doses of beta₂ agonists can be dangerous in some children (see Cautions, below). Excessive use is usually an indication of **inadequately controlled** asthma and should be managed with a prophylactic drug such as an inhaled corticosteroid. The child and the child's carer should be advised to seek medical advice when the prescribed dose of beta₂ agonist fails to provide the usual degree of symptomatic relief because this usually indicates a worsening of the asthma and the child may require alternative medication (see Management of Chronic Asthma table, p. 133).

Children and their carers should be advised to follow manufacturers' instructions on the care and cleansing of inhaler devices.

Nebuliser (or respirator) solutions of salbutamol and terbutaline are used for the treatment of severe acute asthma both in hospital and in general practice. Children with a severe attack of asthma should have oxygen if possible during nebulisation since beta₂ agonists can increase arterial hypoxaemia, see also section 3.1.5.

Oral Oral preparations of beta₂ agonists may be used for children if an inhaler device cannot be used but inhaled beta₂ agonists are more effective and have fewer side-effects. A modified-release formulation of salbutamol may be of value in nocturnal asthma as an alternative to modified-release theophylline preparations (section 3.1.3), but an inhaled long-acting beta₂ agonist is preferable.

Parenteral Beta₂ agonists can be given intravenously in children with severe or life-threatening acute asthma. Chronic asthma unresponsive to stepwise treatment (see Management of Chronic Asthma, p. 133) may benefit from continuous subcutaneous infusion of a beta₂ agonist, but this should be used only under the supervision of a respiratory specialist; the evidence of benefit is uncertain and it may be difficult to withdraw such treatment once started.

Cautions Beta₂ agonists should be used with caution in diabetes—monitor blood glucose (risk of ketoacidosis, especially when a beta₂ agonist is given intravenously). Beta₂ agonists should also be used with caution in hyperthyroidism, cardiovascular disease, arrhythmias, susceptibility to QT-interval prolongation, and hypertension. **Interactions:** Appendix 1 (sympathomimetics, beta₂).

Hypokalaemia Potentially serious hypokalaemia may result from beta₂ agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia. Plasma-potassium concentration should therefore be monitored in severe asthma.

Side-effects Side-effects of the beta₂ agonists include fine tremor (particularly in the hands), nervous tension, headache, peripheral dilatation and palpitation. Other side-effects include tachycardia, arrhythmias, peripheral vasodilation, myocardial ischaemia, and disturbances of sleep and behaviour. Muscle cramps and hypersensitivity reactions including paradoxical bronchospasm (occasionally severe), urticaria, angioedema, hypotension, and collapse have also been reported. High doses of beta₂ agonists are associated with hypokalaemia (see Hypokalaemia, above).

FORMOTEROL FUMARATE (Formoterol fumarate)

Note For use in asthma only in children who regularly use an inhaled corticosteroid, see notes above

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above; nausea, dizziness, rash, taste disturbances, and pruritus also reported

Indications and dose

Reversible airways obstruction (including nocturnal asthma and prevention of exercise-induced bronchospasm) in patients requiring long-term regular bronchodilator therapy see also Management of Chronic Asthma table, p. 133; for dose see preparations below

Counselling Advise children and carers not to exceed prescribed dose, and to follow manufacturer's directions; if a previously effective dose of inhaled formoterol fails to provide adequate relief, a doctor's advice should be obtained as soon as possible

Formoterol (Non-proprietary) (PoM)

Dry powder for inhalation, formoterol fumarate 12 micrograms/metered inhalation, net price 120-dose unit = £23.75. Counselling, administration

Brands include Easyhaler[®] Formoterol

Dose

Chronic asthma

- By inhalation of powder

Child 6–12 years 12 micrograms twice daily

Child 12–18 years 12 micrograms twice daily, increased to 24 micrograms twice daily in more severe airways obstruction

Atimos Modulite[®] (Chiesi) (PoM)

Aerosol inhalation, formoterol fumarate 12 micrograms/metered inhalation, net price 100-dose unit = £30.06. Counselling, administration

Dose

Chronic asthma

- By aerosol inhalation

Child 12–18 years 12 micrograms twice daily, increased to 24 micrograms twice daily in more severe airways obstruction

Foradil[®] (Novartis) (PoM)

Dry powder for inhalation, formoterol fumarate 12 micrograms/capsule, net price 60-cap pack (with inhaler device) = £23.38. Counselling, administration

Dose

Chronic asthma

- By inhalation of powder

Child 6–12 years 12 micrograms twice daily

Child 12–18 years 12 micrograms twice daily, increased to 24 micrograms twice daily in more severe airways obstruction

Oxis[®] (AstraZeneca) (PoM)

Turbohaler[®] (= dry powder inhaler), formoterol fumarate 6 micrograms/inhalation, net price 60-dose unit = £24.80; 12 micrograms/inhalation, 60-dose unit = £24.80. Counselling, administration

Dose

Chronic asthma

- By inhalation of powder

Child 6–18 years 6–12 micrograms 1–2 times daily; occasionally up to 48 micrograms daily may be needed (max. single dose 12 micrograms); reassess treatment if

additional doses required on more than 2 days a week (see also CHM advice above)

Relief of bronchospasm

- By inhalation of powder
Child 6–18 years 6–12 micrograms

Prevention of exercise-induced bronchospasm

- By inhalation of powder
Child 6–18 years 6–12 micrograms before exercise

Compound preparations

For **compound preparations** containing formoterol, see *Flutiform*® and *Symbicort*®, section 3.2

SALBUTAMOL

(Albuterol)

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above; also lactic acidosis with high doses

Licensed use not licensed for use in hyperkalaemia; syrup and tablets not licensed for use in children under 2 years; modified-release tablets not licensed for use in children under 3 years; injection and solution for intravenous infusion not licensed for use in children under 12 years

Indications and dose

Acute asthma

- By aerosol or nebulised solution inhalation
See Management of Acute Asthma, p. 132
- By intravenous injection over 5 minutes (see also Management of Acute Asthma, p. 132)
Child 1 month–2 years 5 micrograms/kg as a single dose
Child 2–18 years 15 micrograms/kg (max. 250 micrograms) as a single dose
- By continuous intravenous infusion
Child 1 month–18 years 1–2 micrograms/kg/minute, adjusted according to response and heart rate up to 5 micrograms/kg/minute; doses above 2 micrograms/kg/minute should be given in an intensive care setting

Exacerbations of reversible airways obstruction (including nocturnal asthma) and prevention of allergen- or exercise-induced bronchospasm, see also Management of Chronic Asthma, p. 133

- By aerosol inhalation
Child 1 month–18 years 100–200 micrograms (1–2 puffs); for persistent symptoms up to 4 times daily
- By inhalation of powder
See under preparations
- By mouth (but use by inhalation preferred)
Child 1 month–2 years 100 micrograms/kg (max. 2 mg) 3–4 times daily
Child 2–6 years 1–2 mg 3–4 times daily
Child 6–12 years 2 mg 3–4 times daily
Child 12–18 years 2–4 mg 3–4 times daily

Severe hyperkalaemia (section 9.2.1.1)

- By intravenous injection over 5 minutes

Neonate 4 micrograms/kg as a single dose; repeat if necessary

Child 1 month–18 years 4 micrograms/kg as a single dose; repeat if necessary

- By inhalation of nebulised solution (but intravenous injection preferred)

Neonate 2.5–5 mg as a single dose; repeat if necessary

Child 1 month–18 years 2.5–5 mg as a single dose; repeat if necessary

Administration for *continuous intravenous infusion*, dilute to a concentration of 200 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%. If fluid-restricted, can be given undiluted through central venous catheter [unlicensed]

For *intravenous injection*, dilute to a concentration of 50 micrograms/mL with Glucose 5%, Sodium Chloride 0.9%, or Water for injections

For *nebulisation*, dilute nebuliser solution with a suitable volume of sterile Sodium Chloride 0.9% solution according to nebuliser type and duration of administration; salbutamol and ipratropium bromide solutions are compatible and can be mixed for nebulisation

Oral

Salbutamol (Non-proprietary) (PoM)

Tablets, salbutamol (as sulfate) 2 mg, net price 28-tab pack = £75.48; 4 mg, 28-tab pack = £77.26

Oral solution, salbutamol (as sulfate) 2 mg/5 mL, net price 150 mL = 72p

Brands include *Salapin*® (sugar-free)

Ventmax® SR (Chiesi) (PoM)

Capsules, m/r, salbutamol (as sulfate) 4 mg (green/grey), net price 56-cap pack = £8.08; 8 mg (white), 56-cap pack = £9.69. Label: 25

Dose

Chronic asthma (but see notes above)

- By mouth

Child 3–12 years 4 mg twice daily

Child 12–18 years 8 mg twice daily

Ventolin® (A&H) (PoM)

Syrup, sugar-free, salbutamol (as sulfate) 2 mg/5 mL, net price 150 mL = 72p

Parenteral

Ventolin® (A&H) (PoM)

Injection, salbutamol (as sulfate) 500 micrograms/mL, net price 1-mL amp = 38p

Solution for intravenous infusion, salbutamol (as sulfate) 1 mg/mL. Dilute before use. Net price 5-mL amp = £2.48

■ Inhalation

Counselling Advise children and carers not to exceed prescribed dose and to follow manufacturer's directions; if a previously effective dose of inhaled salbutamol fails to provide at least 3 hours relief, a doctor's advice should be obtained as soon as possible.

Salbutamol (Non-proprietary) (PoM)

Aerosol inhalation, salbutamol (as sulfate) 100 micrograms/metered inhalation, net price 200-dose unit = £1.50. Counselling, administration

Brands include *AirSalb*®, *Salamol*®

Nebuliser solution, salbutamol (as sulfate) 1 mg/mL, net price 20 × 2.5 mL (2.5 mg) = £1.91; 2 mg/mL, 20 × 2.5 mL (5 mg) = £3.82. May be diluted with sterile sodium chloride 0.9%

Brands include *Salamol Steri-Neb*®

Airomir® (TEVA UK) (PoM)

Aerosol inhalation, salbutamol (as sulfate) 100 micrograms/metered inhalation, net price 200-dose unit = £1.97. Counselling, administration

Autohaler (breath-actuated aerosol inhalation), salbutamol (as sulfate) 100 micrograms/metered inhalation, net price 200-dose unit = £6.02. Counselling, administration

Asmasal Clickhaler® (RPH) (PoM)

Dry powder for inhalation, salbutamol (as sulfate) 95 micrograms/metered inhalation, net price 200-dose unit = £5.65. Counselling, administration

Acute bronchospasm

- By inhalation of powder

Child 5–18 years 1–2 puffs; for persistent symptoms up to 4 times daily (but see also Management of Chronic Asthma, p. 133)

Prophylaxis of allergen- or exercise-induced bronchospasm

- By inhalation of powder

Child 5–18 years 1–2 puffs

Easyhaler® **Salbutamol** (Orion) (PoM)

Dry powder for inhalation, salbutamol (as sulfate) 100 micrograms/metered inhalation, net price 200-dose unit = £3.31; 200 micrograms/metered inhalation, 200-dose unit = £6.63. Counselling, administration

Acute bronchospasm

- By inhalation of powder

Child 5–12 years 100–200 micrograms; max. 800 micrograms daily (but see also Management of Chronic Asthma, p. 133)

Child 12–18 years initially 100–200 micrograms, increased to 400 micrograms if necessary; max. 800 micrograms daily (but see also Management of Chronic Asthma, p. 133)

Prophylaxis of allergen- or exercise-induced bronchospasm

- By inhalation of powder

Child 5–12 years 100–200 micrograms

Child 12–18 years 200 micrograms

Pulvinal® **Salbutamol** (Chiesi) (PoM)

Dry powder for inhalation, salbutamol 200 micrograms/metered inhalation, net price 100-dose unit = £4.85. Counselling, administration

Acute bronchospasm

- By inhalation of powder

Child 5–18 years 200 micrograms; for persistent symptoms up to 800 micrograms daily (but see also Management of Chronic Asthma, p. 133)

Prophylaxis of allergen- or exercise- induced bronchospasm

- By inhalation of powder

Child 5–18 years 200 micrograms

Salamol Easi-Breathe® (TEVA UK) (PoM)

Aerosol inhalation, salbutamol 100 micrograms/metered inhalation, net price 200-dose breath-actuated unit = £6.30. Counselling, administration

Salbulin Novolizer® (Meda) (PoM)

Dry powder for inhalation, salbutamol (as sulfate) 100 micrograms/metered inhalation, net price refillable 200-dose unit = £4.95; 200-dose refill = £2.75. Counselling, administration

Dose

Acute bronchospasm

- By inhalation of powder

Child 6–12 years 100–200 micrograms; for persistent symptoms up to 400 micrograms daily (but see also Management of Chronic Asthma, p. 133)

Child 12–18 years 100–200 micrograms; for persistent symptoms up to 800 micrograms daily (but see also Management of Chronic Asthma, p. 133)

Prophylaxis of allergen- or exercise-induced bronchospasm

- By inhalation of powder

Child 6–12 years 100–200 micrograms

Child 12–18 years 200 micrograms

Ventolin® (A&H) (PoM)

Accuhaler® (dry powder for inhalation), disk containing 60 blisters of salbutamol (as sulfate) 200 micrograms/blister with *Accuhaler*® device, net price = £3.00. Counselling, administration

Dose

Acute bronchospasm

- By inhalation of powder

Child 5–18 years 200 micrograms; for persistent symptoms up to 4 times daily but see also Management of Chronic Asthma, p. 133

Prophylaxis of allergen- or exercise-induced bronchospasm

- By inhalation of powder

Child 5–18 years 200 micrograms

Evohaler® (aerosol inhalation), salbutamol (as sulfate) 100 micrograms/metered inhalation, net price 200-dose unit = £1.50. Counselling, administration

Nebules® (for use with nebuliser), salbutamol (as sulfate) 1 mg/mL, net price 20 × 2.5 mL (2.5 mg) = £1.65; 2 mg/mL, 20 × 2.5 mL (5 mg) = £2.78. May be diluted with sterile sodium chloride 0.9%

Respirator solution (for use with a nebuliser or ventilator), salbutamol (as sulfate) 5 mg/mL. Net price 20 mL = £2.18 (hosp. only). May be diluted with sterile sodium chloride 0.9%

SALMETEROL

Note Not for immediate relief of acute attacks; for use in asthma only in children who regularly use an inhaled corticosteroid, see notes above

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above; nausea, dizziness, arthralgia, and rash also reported

Licensed use *Neovent*® not licensed for use in children under 12 years

Indications and dose

Reversible airways obstruction (including nocturnal asthma and prevention of exercise-induced bronchospasm) in patients requiring long-term regular bronchodilator therapy see also Management of Chronic Asthma, p. 133

• By inhalation

Child 5–12 years 50 micrograms (2 puffs or 1 blister) twice daily

Child 12–18 years 50 micrograms (2 puffs or 1 blister) twice daily; up to 100 micrograms (4 puffs or 2 blisters) twice daily in more severe airways obstruction

Counselling Advise children and carers that salmeterol should **not** be used for relief of acute attacks, not to exceed prescribed dose, and to follow manufacturer's directions; if a previously effective dose of inhaled salmeterol fails to provide adequate relief, a doctor's advice should be obtained as soon as possible

Salmeterol (Non-proprietary) (PoM)

Aerosol inhalation, salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £27.80. Counselling, administration

Brands include *Neovent*

Serevent® (A&H) (PoM)

Accuhaler® (dry powder for inhalation), disk containing 60 blisters of salmeterol (as xinafoate) 50 micrograms/blister with *Accuhaler*® device, net price = £29.26. Counselling, administration

Evohaler® (aerosol inhalation), salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £29.26. Counselling, administration

■ Compound preparations

For **compound preparations** containing salmeterol, see section 3.2

TERBUTALINE SULFATE

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above

Licensed use tablets not licensed for use in children under 7 years; injection not licensed for use in children under 2 years

Indications and dose

Acute asthma

• By inhalation of nebulised solution

See Management of Acute Asthma, p. 132

• By subcutaneous or slow intravenous injection

Child 2–15 years 10 micrograms/kg (max. 300 micrograms) up to 4 times daily

Child 15–18 years 250–500 micrograms up to 4 times daily

• By continuous intravenous infusion

Child 1 month–18 years initially 2–4 micrograms/kg as a loading dose, then 1–10 micrograms/kg/hour according to response and heart rate (doses above 10 micrograms/kg/hour with close monitoring)

Exacerbations of reversible airways obstruction (including nocturnal asthma) and prevention of exercise-induced bronchospasm see Management of Chronic Asthma table, p. 133

• By inhalation of powder

Child 5–18 years 500 micrograms (1 inhalation) up to 4 times daily (for occasional use only)

• By mouth (but not recommended)

Child 1 month–7 years 75 micrograms/kg (max. 2.5 mg) 3 times daily

Child 7–15 years 2.5 mg 2–3 times daily

Child 15–18 years initially 2.5 mg 3 times daily, increased if necessary to 5 mg 3 times daily

Administration For *continuous intravenous infusion*, dilute to a concentration of 5 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; if fluid-restricted, dilute to a concentration of 100 micrograms/mL

For *nebulisation*, dilute nebuliser solution with sterile Sodium Chloride 0.9% solution according to nebuliser type and duration of administration; terbutaline and ipratropium bromide solutions are compatible and may be mixed for nebulisation.

■ Oral and parenteral

Bricanyl® (AstraZeneca) (PoM)

Tablets, scored, terbutaline sulfate 5 mg, net price 100-tab pack = £4.91

Syrup, sugar-free, terbutaline sulfate 1.5 mg/5 mL, net price 100 mL = £2.80

Injection, terbutaline sulfate 500 micrograms/mL, net price 1-mL amp = 43p; 5-mL amp = £1.67

■ Inhalation

Counselling Advise children and carers not to exceed prescribed dose and to follow manufacturer's directions; if a previously effective dose of inhaled terbutaline fails to provide at least 3 hours relief, a doctor's advice should be obtained as soon as possible

Bricanyl® (AstraZeneca) (PoM)

Turbohaler® (= dry powder inhaler), terbutaline sulfate 500 micrograms/metered inhalation, net price 100-dose unit = £6.92. Counselling, administration

Respules® (= single-dose units for nebulisation), terbutaline sulfate 2.5 mg/mL, net price 20 × 2-mL units (5 mg) = £5.82

3.1.1.2 Other adrenoceptor agonists

Adrenaline (epinephrine) injection (1 in 1000) is used in the emergency treatment of acute allergic and anaphylactic reactions (section 3.4.3), in angioedema (section 3.4.3), and in cardiopulmonary resuscitation (section 2.7.3). Adrenaline solution (1 in 1000) is used by nebulisation in the management of severe croup (section 3.1).

3.1.2 Antimuscarinic bronchodilators

Ipratropium by nebulisation can be added to other standard treatment in life-threatening acute asthma or if acute asthma fails to improve with standard therapy (see Management of Acute Asthma, p. 132). Ipratropium can be used to provide short-term relief in chronic

asthma, but short-acting beta₂ agonists act more quickly and are preferred.

The aerosol inhalation of ipratropium has a maximum effect 30–60 minutes after use; its duration of action is 3 to 6 hours.

IPRATROPIUM BROMIDE

Cautions risk of glaucoma (see below), bladder outflow obstruction; cystic fibrosis; **interactions:** Appendix 1 (antimuscarinics)

Glaucoma *Acute angle-closure glaucoma* has been reported with nebulised ipratropium, particularly when given with nebulised salbutamol (and possibly other beta₂ agonists); care needed to protect the child's eyes from nebulised drug or from drug powder

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects dry mouth, nausea, gastro-intestinal motility disorder (including constipation and diarrhoea), throat irritation, cough, headache, dizziness; *less commonly* vomiting, stomatitis, palpitation, tachycardia, bronchospasm (including paradoxical bronchospasm), laryngospasm, pharyngeal oedema, urinary retention, mydriasis, angle-closure glaucoma, pruritus; *rarely* atrial fibrillation, ocular accommodation disorder

Indications and dose

Acute asthma

- By inhalation of nebulised solution
See Management of Acute Asthma, section 3.1

Reversible airways obstruction

- By aerosol inhalation

Child 1 month–6 years 20 micrograms 3 times daily

Child 6–12 years 20–40 micrograms 3 times daily

Child 12–18 years 20–40 micrograms 3–4 times daily

Counselling Advise child and carer not to exceed prescribed dose and to follow manufacturer's directions

Rhinitis section 12.2.2

Ipratropium Bromide (Non-proprietary) (POM)

Nebuliser solution, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL (250-microgram) unit-dose vials = £4.39, 60 × 1-mL = £21.78; 20 × 2-mL (500-microgram) = £5.23, 60 × 2-mL = £26.97

Atrovent® (Boehringer Ingelheim) (POM)

Aerosol inhalation, ipratropium bromide 20 micrograms/metered inhalation, net price 200-dose unit = £5.56. Counselling, administration

Nebuliser solution, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL unit-dose vials = £4.14, 60 × 1-mL vials = £12.44; 20 × 2-mL vials = £4.87, 60 × 2-mL vials = £14.59

Ipratropium Steri-Neb® (TEVA UK) (POM)

Nebuliser solution, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL (250-microgram) unit-dose vials = £14.99; 20 × 2-mL (500-microgram) = £15.99

Respontin® (A&H) (POM)

Nebuliser solution, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL (250-microgram) unit-dose vials = £4.78; 20 × 2-mL (500-microgram) = £5.60

3.1.3 Theophylline

Theophylline is a xanthine used as a bronchodilator in asthma, see Management of Chronic Asthma p. 133. It may have an additive effect when used in conjunction with small doses of beta₂ agonists; the combination may increase the risk of side-effects, including hypokalaemia (see p. 136).

Theophylline is given by injection as **aminophylline**, a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone. Aminophylline injection is needed rarely for severe acute asthma (see Management of Acute Asthma p. 134). It must be given by **very slow** intravenous injection (over at least 20 minutes) or by intravenous infusion; it is too irritant for intramuscular use. Measurement of plasma-theophylline concentration may be helpful and is **essential** if a loading dose of aminophylline is to be given to children who are already taking theophylline, because serious side-effects such as convulsions and arrhythmias can occasionally precede other symptoms of toxicity.

Theophylline is metabolised in the liver. The plasma-theophylline concentration is *increased* in heart failure, hepatic impairment, viral infections, and by drugs that inhibit its metabolism. The plasma-theophylline concentration is *decreased* in smokers, by alcohol consumption, and by drugs that induce its metabolism. For interactions of theophylline, see Appendix 1.

Plasma-theophylline concentration In most individuals a plasma-theophylline concentration of 10–20 mg/litre (55–110 micromol/litre) is required for satisfactory bronchodilation, but a lower concentration of 5–15 mg/litre may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase if the concentration exceeds 20 mg/litre.

Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment. A blood sample should usually be taken 4–6 hours after an oral dose of a modified-release preparation (sampling times may vary—consult local guidelines). If aminophylline is given intravenously, a blood sample should be taken 4–6 hours after starting treatment.

THEOPHYLLINE

Cautions see notes above; also cardiac arrhythmias or other cardiac disease, hypertension, hyperthyroidism; peptic ulcer; epilepsy; fever; hypokalaemia risk, p. 136; monitor plasma-theophylline concentration (see notes above); dose adjustment may be necessary if smoking started or stopped during treatment; **interactions:** Appendix 1 (theophylline) and notes above

Hepatic impairment reduce dose

Pregnancy neonatal irritability and apnoea reported; see also p. 131

Breast-feeding present in milk—irritability in infant reported; modified-release preparations preferable; see also p. 131

Side-effects nausea, vomiting, gastric irritation, diarrhoea, palpitation, tachycardia, arrhythmias, headache, CNS stimulation, insomnia, convulsions **overdose:** see Emergency Treatment of Poisoning, p. 30

Licensed use *Slo-Phyllin*® capsules not licensed for use in children under 2 years

Indications and dose**Chronic asthma**

See under preparations below and Management of Chronic Asthma table, p. 133

Note Plasma-theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); narrow margin between therapeutic and toxic dose, see also notes above

Modified release

Note The rate of absorption from modified-release preparations can vary between different brands. If a prescription for a modified-release oral theophylline preparation does not specify a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a child discharged from hospital should be maintained on the brand on which that child was stabilised as an in-patient.

Nuelin SA[®] (Meda)

SA tablets, m/r, theophylline 175 mg. Net price 60-tab pack = £6.38. Label: 21, 25

Dose**Chronic asthma**

- By mouth

Child 6–12 years 175 mg every 12 hours

Child 12–18 years 175–350 mg every 12 hours

SA 250 tablets, m/r, scored, theophylline 250 mg.

Net price 60-tab pack = £8.92. Label: 21, 25

Dose**Chronic asthma**

- By mouth

Child 6–12 years 125–250 mg every 12 hours

Child 12–18 years 250–500 mg every 12 hours

Slo-Phyllin[®] (Merck Serono)

Capsules, m/r, theophylline 60 mg (white/clear, enclosing white pellets), net price 56-cap pack = £2.76; 125 mg (brown/clear, enclosing white pellets), 56-cap pack = £3.48; 250 mg (purple/clear, enclosing white pellets), 56-cap pack = £4.34. Label: 25, or counselling, see below

Dose**Chronic asthma**

- By mouth

Child 6 months–2 years 12 mg/kg (max. 120 mg) every 12 hours

Child 2–6 years 60–120 mg every 12 hours

Child 6–12 years 125–250 mg every 12 hours

Child 12–18 years 250–500 mg every 12 hours

Administration Contents of the capsule (enteric-coated granules) may be sprinkled on to a spoonful of soft food (e.g. yoghurt) and swallowed without chewing

Uniphyllin Continus[®] (Napp)

Tablets, m/r, theophylline 200 mg, net price 56-tab pack = £2.96; 300 mg, 56-tab pack = £4.77; 400 mg, 56-tab pack = £5.65. Label: 25

Dose**Chronic asthma**

- By mouth

Child 2–12 years 9 mg/kg (max. 200 mg) every 12 hours; some children with chronic asthma may require 10–16 mg/kg (max. 400 mg) every 12 hours

Child 12–18 years 200 mg every 12 hours, increased according to response to 400 mg every 12 hours

Note May be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in children whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as a single evening or morning dose

AMINOPHYLLINE

Note Aminophylline is a stable mixture or combination of theophylline and ethylenediamine; the ethylenediamine confers greater solubility in water

Cautions see under Theophylline; also rapid intravenous injection can cause arrhythmias

Hepatic impairment see under Theophylline

Pregnancy see under Theophylline

Breast-feeding see under Theophylline

Side-effects see under Theophylline; also allergy to ethylenediamine can cause urticaria, erythema, and exfoliative dermatitis; hypotension, arrhythmias, and convulsions, especially if given rapidly by intravenous injection

Licensed use Aminophylline injection not licensed for use in children under 6 months; *Phyllocontin Continus[®]* Forte tablets are not licensed for use in children

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Chronic asthma (see also Management of Chronic Asthma, p. 133)

- By mouth

See under preparations below

Severe acute asthma not previously treated with theophylline (with close monitoring; see also Management of Acute Asthma, section 3.1)

- By intravenous injection over at least 20 minutes

Child 1 month–18 years 5 mg/kg (max. 500 mg) then by intravenous infusion

Severe acute asthma (with close monitoring; see also Management of Acute Asthma, section 3.1)

- By intravenous infusion

Child 1 month–12 years 1 mg/kg/hour adjusted according to plasma-theophylline concentration

Child 12–18 years 500–700 micrograms/kg/hour adjusted according to plasma-theophylline concentration

Note Plasma-theophylline concentration for optimum response in asthma 10–20 mg/litre (55–110 micromol/litre); narrow margin between therapeutic and toxic dose; children taking oral theophylline or aminophylline should not normally receive a loading dose of intravenous aminophylline; it is recommended that plasma-theophylline concentration is measured in all children receiving intravenous aminophylline (see notes above)

Administration For intravenous infusion, dilute to a concentration of 1 mg/mL with Glucose 5% or Sodium Chloride 0.9%

Aminophylline (Non-proprietary) (PoM)

Injection, aminophylline 25 mg/mL, net price 10-mL amp = 65p

Modified release

Note Advice about modified-release theophylline preparations above also applies to modified-release aminophylline preparations

Phyllocontin Continus[®] (Napp)

Tablets, m/r, yellow, f/c, aminophylline hydrate 225 mg, net price 56-tab pack = £2.40; 350 mg (Forte tablets) 56-tab pack = £4.22. Label: 25 Dose

Chronic asthma (see also Management of Chronic Asthma, p. 133)

- **By mouth**

Child body-weight over 40 kg initially 225 mg twice daily, increased after 1 week to 450 mg twice daily according to plasma-theophylline concentration

Personal Best[®], range 60–800 litres/minute, net price = £6.86 (Resprionics)

Piko-1[®], range 15–999 litres/minute, net price = £9.50, replacement mouthpiece = 38p (nSPIRE Health)

Pinnacle[®], range 60–900 litres/minute, net price = £6.50 (Fyne Dynamics)

Pocketpeak[®], range 60–800 litres/minute, net price = £6.53, replacement mouthpiece = 38p (nSPIRE Health)

Vitalograph[®], range 50–800 litres/minute, net price = £4.83 (a child's peak flow meter is also available) (Vitalograph)

Low Range Peak Flow Meter

Compliant to standard EN ISO 23747: 2007 except for scale range

Medi[®], range 40–420 litres/minute, net price = £6.50 (Medicare)

Mini-Wright[®], range 30–400 litres/minute, net price = £7.04, replacement mouthpiece = 38p (Clement Clarke)

Pocketpeak[®], range 50–400 litres/minute, net price = £6.53, replacement mouthpiece = 38p (nSPIRE Health)

3.1.4 Compound bronchodilator preparations

In general, children are best treated with single-ingredient preparations, such as a selective beta₂ agonist (section 3.1.1.1) or ipratropium bromide (section 3.1.2), so that the dose of each drug can be adjusted. This flexibility is lost with compound bronchodilator preparations.

3.1.5 Peak flow meters, inhaler devices, and nebulisers

Peak flow meters

Peak flow meters may be used to assess lung function in children over 5 years with asthma, but symptom monitoring is the most reliable assessment of asthma control. They are best used for short periods to assess the severity of asthma and to monitor response to treatment; continuous use of peak flow meters may detract from compliance with inhalers.

Peak flow charts should be issued where appropriate, and are available to purchase from:

3M Security Print and Systems Limited
Gorse Street, Chadderton
Oldham,
OL9 9QH

Tel: 0845 610 1112

GP practices can obtain supplies through their Area Team stores.

NHS Hospitals can order supplies from www.nhsforms.co.uk or by emailing nhsforms@mmm.com.

In Scotland, peak flow charts can be obtained by emailing stockorders.dppas@apsgroup.co.uk.

Standard Range Peak Flow Meter

Conforms to standard EN ISO 23747: 2007

AirZone[®], range 60–720 litres/minute, net price = £4.63, replacement mouthpiece = 38p (Clement Clarke)

Medi[®], range 60–800 litres/minute, net price = £4.50 (Medicare)

MicroPeak[®], range 60–900 litres/minute, net price = £6.50, replacement mouthpiece = 38p (Micro Medical)

Mini-Wright[®], range 60–800 litres/minute, net price = £6.99, replacement mouthpiece = 38p (Clement Clarke)

Drug delivery devices

Inhaler devices A *pressurised metered-dose inhaler* is an effective method of drug administration in mild to moderate chronic asthma; to deliver the drug effectively, a spacer device should also be used (see also NICE guidance, below). By the age of 3 years, a child can usually be taught to use a spacer device without a mask. As soon as a child is able to use the mouthpiece, then this is the preferred delivery system.

Dry powder inhalers may be useful in children over 5 years, who are unwilling or unable to use a pressurised metered-dose inhaler with a spacer device; *breath-actuated inhalers* may be useful in older children if they are able to use the device effectively. The child or child's carer should be instructed carefully on the use of the inhaler. It is important to check that the inhaler is being used correctly; poor inhalation technique may be mistaken for a lack of response to the drug.

On changing from a pressurised metered-dose inhaler to a dry powder inhaler, the child may notice a lack of sensation in the mouth and throat previously associated with each actuation; coughing may occur more frequently following use of a dry-powder inhaler.

CFC-free metered-dose inhalers should be cleaned **weekly** according to the manufacturer's instructions.

NICE guidance**Inhaler devices for children under 5 years with chronic asthma (August 2000)**

A child's needs and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

- corticosteroid and bronchodilator therapy should be delivered by pressurised metered-dose inhaler and spacer device, with a facemask if necessary;
- if this is not effective, and depending on the child's condition, nebulised therapy may be considered and, in children over 3 years, a dry powder inhaler may also be considered [but see notes above].

www.nice.org.uk/TA10

NICE guidance**Inhaler devices for children 5–15 years with chronic asthma (March 2002)**

A child's needs, ability to develop and maintain effective technique, and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

- corticosteroid therapy should be routinely delivered by a pressurised metered-dose inhaler and spacer device;
- for other inhaled drugs, particularly bronchodilators, a wider range of devices should be considered;
- children and their carers should be trained in the use of the chosen device; suitability of the device should be reviewed at least annually. Inhaler technique and compliance should be monitored.

www.nice.org.uk/TA38

Spacer devices Spacer devices are particularly useful for infants, for children with poor inhalation technique, or for nocturnal asthma, because the device reduces the need for coordination between actuation of a pressurised metered-dose inhaler and inhalation. The spacer device reduces the velocity of the aerosol and subsequent impaction on the oropharynx and allows more time for evaporation of the propellant so that a larger proportion of the particles can be inhaled and deposited in the lungs. Smaller-volume spacers may be more manageable for pre-school children and infants. The spacer device used must be compatible with the prescribed metered-dose inhaler.

Use and care of spacer devices The suitability of the spacer device should be carefully assessed; opening the one-way valve is dependent on the child's inspiratory flow. Some devices can be tipped to 45° to open the valve during inhaler actuation and inspiration to assist the child.

Inhalation from the spacer device should follow the actuation as soon as possible because the drug aerosol is very short-lived. The total dose (which may be more than a single puff) should be administered as single actuations (with tidal breathing for 10–20 seconds or 5 breaths for each actuation) for children with good inspiratory flow. Larger doses may be necessary for a child with acute bronchospasm; for guidance on the Management of Acute Asthma, see section 3.1.

The device should be cleansed once a month by washing in mild detergent and then allowed to dry in air without rinsing; the mouthpiece should be wiped clean of detergent before use. Some manufacturers recommend more frequent cleaning, but this should be avoided since any electrostatic charge may affect drug delivery. Spacer devices should be replaced every 6–12 months.

A2A Spacer® (Clement Clarke)

Spacer device, for use with all pressurised (aerosol) inhalers, net price = £4.15; with small or medium mask = £6.68

Able Spacer® (Clement Clarke)

Spacer device, small-volume device. For use with all pressurised (aerosol) inhalers, net price standard device = £4.33; with infant or child mask = £7.06

AeroChamber® Plus (GSK)

Spacer device, medium-volume device. For use with all pressurised (aerosol) inhalers, net price standard device (blue) = £4.75, with mask (blue) = £7.92; infant device (orange) with mask = £7.92; child device (yellow) with mask = £7.92

Babyhaler® (A&H) 

Spacer device, paediatric use with *Flixotide®*, and *Ventolin®* inhalers, net price = £11.34

Haleraid® (A&H)

Inhalation aid, device to place over pressurised (aerosol) inhalers to aid when strength in hands is impaired (e.g. arthritis). For use with *Flixotide®*, *Sereotide®*, *Serevent®*, and *Ventolin®* inhalers. Available as *Haleraid® 120* for 120-dose inhalers and *Haleraid® 200* for 200-dose inhalers, net price = 80p

OptiChamber® (Respironics)

Spacer device, for use with all pressurised (aerosol) inhalers, net price = £4.28

OptiChamber® Diamond (Respironics)

Spacer device, for use with all pressurised (aerosol) inhalers, net price = £4.49; with small, medium, or large mask = £7.49

Pocket Chamber® (nSPIRE Health)

Spacer device, small-volume device. For use with all pressurised (aerosol) inhalers, net price = £4.18; with infant, small, medium, or large mask = £9.75


Space Chamber Plus® (Medical Developments)

Spacer device, for use with all pressurised (aerosol) inhalers, net price standard device = £4.26; compact device = £4.26

Volumatic® (A&H)

Spacer inhaler, large-volume device. For use with *Clenil Modulite®*, *Flixotide®*, *Seretide®*, *Serevent®*, and *Ventolin®* inhalers, net price = £3.81; with paediatric mask = £6.70

Vortex® (Pari)

Spacer device, medium-volume device. For use with all pressurised (aerosol) inhalers, net price with mouthpiece = £6.28; with mask for infant or child = £7.99; with adult mask = £9.97 

Nebulisers

In England and Wales nebulisers and compressors are not available on the NHS (but they are free of VAT); some nebulisers (but not compressors) are available on form GP10A in Scotland (for details consult Scottish Drug Tariff).

A nebuliser converts a solution of a drug into an aerosol for inhalation. It is used to deliver higher doses of drug to the airways than is usual with standard inhalers. The main indications for use of a nebuliser are:

- to deliver a beta₂ agonist or ipratropium to a child with an *acute exacerbation* of asthma or of airways obstruction;
- to deliver *prophylactic medication* to a child unable to use other conventional devices;

- to deliver an antibacterial (such as colistimethate sodium or tobramycin) to a child with chronic purulent infection (as in cystic fibrosis or bronchiectasis);
- to deliver budesonide to a child with severe croup.

The proportion of a nebuliser solution that reaches the lungs depends on the type of nebuliser and although it can be as high as 30% it is more frequently close to 10% and sometimes below 10%. The remaining solution is left in the nebuliser as residual volume or it is deposited in the mouthpiece and tubing. The extent to which the nebulised solution is deposited in the airways or alveoli depends on particle size. Particles with a median diameter of 1–5 microns are deposited in the airways and are therefore appropriate for asthma whereas a particle size of 1–2 microns is needed for alveolar deposition. The type of nebuliser is therefore chosen according to the deposition required and according to the viscosity of the solution.

Some jet nebulisers are able to increase drug output during inspiration and hence increase efficiency.

Nebulised bronchodilators are appropriate for children with chronic persistent asthma or those with severe acute asthma. In chronic asthma, nebulised bronchodilators should only be used to relieve persistent daily wheeze, however, with the development of spacers with facemasks, it is now unusual for a child to require long-term nebulised asthma therapy (see Management of Chronic Asthma table, p. 133). The use of nebulisers in chronic persistent asthma should be considered only:

- after a review of the diagnosis and use of current inhaler devices;
- if the airflow obstruction is significantly reversible by bronchodilators without unacceptable side-effects;
- if the child does not benefit from use of conventional inhaler device, such as pressurised metered-dose inhaler plus spacer;
- if the child is complying with the prescribed dose and frequency of anti-inflammatory treatment including regular use of high-dose inhaled corticosteroid.

When a nebuliser is prescribed, the child or child's carer must:

- have clear instructions from a doctor, specialist nurse, physiotherapist, or pharmacist on the use of the nebuliser (and on peak-flow monitoring—see notes above);
- be instructed not to treat acute attacks without also seeking medical help;
- have regular follow up with doctor or specialist nurse.

Jet nebulisers are more widely used than ultrasonic nebulisers. Most jet nebulisers require an optimum flow rate of 6–8 litres/minute and in hospital can be driven by piped air or oxygen; in acute asthma the nebuliser should always be driven by oxygen. Domiciliary oxygen cylinders do not provide an adequate flow rate therefore an electrical compressor is required for domiciliary use.

Safe practice

The Department of Health has reminded users of the need to use the correct grade of tubing when connecting a nebuliser to a medical gas supply or compressor.

Nebuliser diluent

Nebulisation may be carried out using an undiluted nebuliser solution or it may require dilution beforehand. The usual diluent is sterile sodium chloride 0.9% (physiological saline).

Sodium Chloride (Non-proprietary) (PoM)

Nebuliser solution, sodium chloride 0.9%, net price 20 × 2.5 mL = £20.60

Brands include *Saline Steripoule*®, *Saline Steri-Neb*®

3.2 Corticosteroids

Corticosteroids are effective in the management of *asthma*; they reduce airway inflammation.

An inhaled corticosteroid is used regularly for prophylaxis of asthma when a child requires a beta₂ agonist more than twice a week, or if symptoms disturb sleep at least once a week, or if the child has suffered an exacerbation in the last 2 years requiring a systemic corticosteroid (see Management of Chronic Asthma table, p. 133).

Current or previous smoking reduces the effectiveness of inhaled corticosteroids and higher doses may be necessary.

Corticosteroid inhalers must be used regularly for maximum benefit; alleviation of symptoms usually occurs 3 to 7 days after initiation but may take longer. **Beclomethasone dipropionate**, **budesonide**, **fluticasone propionate**, and **mometasone furoate** appear to be equally effective. A spacer device should be used for administering inhaled corticosteroids in children under 15 years (see NICE guidance, section 3.1.5); a spacer device is also useful in children over 15 years, particularly if high doses are required.

In children 12–18 years using an inhaled corticosteroid and a long-acting beta₂ agonist for the prophylaxis of asthma, but who are poorly controlled, (see step 3 of the Management of Chronic Asthma table, p. 133) *Symbicort*® (budesonide with formoterol) may be used as a reliever (instead of a short-acting beta₂ agonist), in addition to its regular use for the prophylaxis of asthma [unlicensed]. *Symbicort*® can also be used in this way in children 12–18 years using an inhaled corticosteroid with a dose greater than 400 micrograms beclomethasone dipropionate daily¹, but who are poorly controlled [unlicensed] (see step 2 of the Management of Chronic Asthma table, p. 133). When starting this treatment, the total regular dose of inhaled corticosteroid should not be reduced. Children and their carers must be carefully instructed on the appropriate dose and management of exacerbations before initiating this treatment, preferably

1. For standard doses of other inhaled corticosteroids, see Management of Chronic Asthma table, p. 133

by a respiratory specialist. Children using budesonide with formoterol as a reliever once a day or more should have their treatment reviewed regularly; see also Side-effects below. This management approach has not been investigated with combination inhalers containing other corticosteroids and long-acting beta₂ agonists.

High doses of inhaled corticosteroids can be prescribed for children who respond only partially to standard doses of an inhaled corticosteroid and a long-acting beta₂ agonist or to other long-acting bronchodilators (see Management of Chronic Asthma table, p. 133). High doses should be continued only if there is clear benefit over the lower dose. The recommended maximum dose of an inhaled corticosteroid should not generally be exceeded; however, if a higher dose is required it should be initiated and supervised by a respiratory paediatrician. The use of high doses of an inhaled corticosteroid can minimise the requirement for an oral corticosteroid (see also Side-effects of Inhaled Corticosteroids, below).

Cautions of inhaled corticosteroids Systemic therapy may be required during periods of stress, such as during severe infections, or when airways obstruction or mucus prevent drug access to smaller airways; **interactions:** Appendix 1 (corticosteroids).

Paradoxical bronchospasm The potential for paradoxical bronchospasm (calling for discontinuation and alternative therapy) should be borne in mind—mild bronchospasm may be prevented by inhalation of a short-acting beta₂ agonist beforehand (or by transfer from an aerosol inhalation to a dry powder inhalation if suitable).

CFC-free inhalers Chlorofluorocarbon (CFC) propellants in pressurised aerosol inhalers have been replaced by hydrofluoroalkane (HFA) propellants.

Doses for corticosteroid CFC-free inhalers may be different from traditional CFC-containing inhalers and may differ between brands, see MHRA/CHM advice below.

MHRA/CHM advice (July 2008)

Beclometasone dipropionate CFC-free pressurised metered-dose inhalers (*Qvar*® and *Clenil Modulite*®) are **not** interchangeable and should be prescribed by brand name; *Qvar*® has extra-fine particles, is more potent than traditional beclometasone dipropionate CFC-containing inhalers, and is approximately twice as potent as *Clenil Modulite*®.

Side-effects of inhaled corticosteroids Inhaled corticosteroids have considerably fewer systemic effects than oral corticosteroids, but adverse effects have been reported.

High doses of inhaled corticosteroids (see Management of Chronic Asthma table, p. 133) used for prolonged periods can induce adrenal suppression. Inhaled corticosteroids have occasionally been associated with adrenal crisis and coma in children; excessive doses should be **avoided**. Children using high doses of inhaled corticosteroids should be under the supervision of a specialist respiratory paediatrician for the duration of the treatment. Consider giving a 'steroid card' (section 6.3.2) to support communication of the risks associated with treatment, and specific written advice to consider corticosteroid replacement during an episode of stress,

such as a severe intercurrent illness or an operation, to children using greater than maximum licensed doses of inhaled corticosteroids. Use of other corticosteroid therapy (including topical) or concurrent use of drugs which inhibit corticosteroid metabolism should be taken into account when assessing systemic risk.

In adults, bone mineral density is sometimes reduced following long-term inhalation of higher doses of corticosteroids, predisposing patients to osteoporosis (section 6.6). It is, therefore, sensible to ensure that the dose of an inhaled corticosteroid is no higher than necessary to keep a child's asthma under good control.

Growth restriction associated with systemic corticosteroid therapy does not seem to occur with recommended doses of inhaled corticosteroids; although initial growth velocity may be reduced, there appears to be no effect on achieving normal adult height. However, the height and weight of children receiving prolonged treatment with inhaled corticosteroid should be monitored annually; if growth is slowed, referral to a paediatrician should be considered.

Hoarseness, dysphonia, throat irritation, and candidiasis of the mouth or throat may occur with inhaled corticosteroids (see Candidiasis below). Paradoxical bronchospasm has been reported very rarely. Anxiety, depression, sleep disturbances, behavioural changes including hyperactivity, irritability, and aggression have been reported; hyperglycaemia (usually only with high doses), skin thinning, and bruising have also been reported.

Candidiasis The risk of oral candidiasis can be reduced by using a spacer device with the corticosteroid inhaler; rinsing the mouth with water after inhalation of a dose may also be helpful. Antifungal oral suspension or oral gel (section 12.3.2) can be used to treat oral candidiasis while continuing corticosteroid therapy.

Oral An acute attack of asthma should be treated with a short course (3–5 days) of oral corticosteroid, see Management of Acute Asthma, p. 132. The dose can usually be stopped abruptly but it should be reduced gradually in children under 12 years who have taken corticosteroids for more than 14 days. Tapering is not needed in children 12–18 years provided that the child receives an inhaled corticosteroid in an adequate dose (apart from those on maintenance oral corticosteroid treatment or where oral corticosteroids are required for 3 or more weeks); see also Withdrawal of Corticosteroids, section 6.3.2.

In chronic continuing asthma, when the response to other drugs has been inadequate, longer term administration of an oral corticosteroid may be necessary; in such cases high doses of an inhaled corticosteroid should be continued to minimise oral corticosteroid requirements.

An oral corticosteroid should normally be taken as a single dose in the morning to reduce the disturbance to circadian cortisol secretion. Dosage should always be titrated to the lowest dose that controls symptoms. Some clinicians use alternate-day dosing of an oral corticosteroid.

Parenteral For the use of hydrocortisone injection in the emergency treatment of acute severe asthma, see Management of Acute Asthma, p. 132.

NICE guidance**Inhaled corticosteroids for the treatment of chronic asthma in children under 12 years (November 2007)**

For children under 12 years with chronic asthma in whom treatment with an inhaled corticosteroid is considered appropriate, the least costly product that is suitable for an individual child (taking into consideration NICE TAs 38 and 10), within its marketing authorisation, is recommended.

For children under 12 years with chronic asthma in whom treatment with an inhaled corticosteroid and a long-acting β_2 agonist is considered appropriate, the following apply:

- the use of a combination inhaler within its marketing authorisation is recommended as an option;
- the decision to use a combination inhaler or two agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence;
- if a combination inhaler is chosen, then the least costly inhaler that is suitable for the individual child is recommended.

www.nice.org.uk/TA131

NICE guidance**Inhaled corticosteroids for the treatment of chronic asthma in children over 12 years (March 2008)**

For children over 12 years with chronic asthma in whom treatment with an inhaled corticosteroid is considered appropriate, the least costly product that is suitable for an individual child (taking into consideration NICE TAs 38 and 10), within its marketing authorisation, is recommended.

For children over 12 years with chronic asthma in whom treatment with an inhaled corticosteroid and a long-acting β_2 agonist is considered appropriate, the following apply:

- the use of a combination inhaler within its marketing authorisation is recommended as an option;
- the decision to use a combination inhaler or two agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence;
- if a combination inhaler is chosen, then the least costly inhaler that is suitable for the individual child is recommended.

www.nice.org.uk/TA138

BECLOMETASONE DIPROPIONATE

(Beclomethasone Dipropionate)

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above

Licensed use *Clenil Modulite*® 200 and -250, and *Qvar*® are not licensed for use in children under 12 years; *Easyhaler*® *Beclomethasone Dipropionate* is not licensed for use in children under 18 years

Indications and dose**Prophylaxis of asthma**

See Management of Chronic Asthma table, p. 133

Important for *Asmabec Clickhaler*®, *Clenil*®, and *Qvar*® doses, see under preparations below

Beclomethasone (Non-proprietary) (PoM)

Dry powder for inhalation, beclomethasone dipropionate 100 micrograms/metered inhalation, net price 100-dose unit = £5.36; 200 micrograms/metered inhalation, 100-dose unit = £9.89, 200-dose unit = £14.93; 400 micrograms/metered inhalation, 100-dose unit = £19.61. Label: 8, counselling, administration; also 10 and steroid card with high doses

Brands include *Pulvinol*® *Beclomethasone Dipropionate*, *Easyhaler*® *Beclomethasone Dipropionate*

Asmabec Clickhaler® (RPH) (PoM)

Dry powder for inhalation, beclomethasone dipropionate 100 micrograms/metered inhalation, net price 200-dose unit = £9.81; 250 micrograms/metered inhalation, 100-dose unit = £12.31. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose**Prophylaxis of asthma**

- **By inhalation of powder**

Child 6–12 years 100–200 micrograms twice daily, adjusted as necessary

Child 12–18 years 100–400 micrograms twice daily, adjusted as necessary; max. 1 mg twice daily

Clenil Modulite® (Chiesi) (PoM)

Aerosol inhalation, beclomethasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £3.70; 100 micrograms/metered inhalation = £7.42; 200 micrograms/metered inhalation = £16.17; 250 micrograms/metered inhalation = £16.29. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose**Prophylaxis of asthma**

- **By aerosol inhalation**

Child 2–12 years 100–200 micrograms twice daily

Child 12–18 years 200–400 micrograms twice daily adjusted as necessary up to 1 mg twice daily

Note *Clenil Modulite*® is not interchangeable with other CFC-free beclomethasone dipropionate inhalers; the MHRA has advised (July 2008) that CFC-free beclomethasone dipropionate inhalers should be prescribed by brand name, see p. 145

Dental Prescribing on NHS *Clenil Modulite*® 50 micrograms/metered inhalation may be prescribed

Qvar® (TEVA UK) (PoM)

Aerosol inhalation, beclomethasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £7.87; 100 micrograms/metered inhalation, 200-dose unit = £17.21. Label: 8, counselling, administration; also 10 and steroid card with high doses

Autohaler® (breath-actuated aerosol inhalation), beclomethasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £7.87; 100 micrograms/metered inhalation, 200-dose unit = £17.21. Label: 8, counselling, administration; also 10 and steroid card with high doses

Easi-Breathe® (breath-actuated aerosol inhalation), beclomethasone dipropionate 50 micrograms/metered inhalation, net price 200-dose = £7.74;

100 micrograms/metered inhalation, 200-dose = £16.95. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose

Prophylaxis of asthma

• By aerosol inhalation

Child 12–18 years 50–200 micrograms twice daily, increased if necessary to max. 400 micrograms twice daily

Important When switching a child with well-controlled asthma from another corticosteroid inhaler, initially a 100-microgram metered dose of *Qvar*® should be prescribed for:

- 200–250 micrograms of beclometasone dipropionate or budesonide
 - 100 micrograms of fluticasone propionate
- When switching a child with poorly controlled asthma from another corticosteroid inhaler, initially a 100-microgram metered dose of *Qvar*® should be prescribed for 100 micrograms of beclometasone dipropionate, budesonide, or fluticasone propionate; the dose of *Qvar*® should be adjusted according to response

Note *Qvar*® is not interchangeable with other CFC-free beclometasone dipropionate inhalers; the MHRA has advised (July 2008) that beclometasone dipropionate CFC-free inhalers should be prescribed by brand name, see p. 145

BUDESONIDE

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above

Licensed use *Pulmicort*® nebuliser solution not licensed for use in children under 3 months; not licensed for use in bronchopulmonary dysplasia; *Symbicort*® not licensed for use in children for asthma maintenance and reliever therapy

Indications and dose

Prophylaxis of asthma see Management of Chronic Asthma table, p. 133, and preparations below

Croup

• By inhalation of nebuliser suspension

Child over 1 month 2 mg as single dose or in 2 divided doses separated by 30 minutes; dose may be repeated every 12 hours until clinical improvement

Bronchopulmonary dysplasia with spontaneous respiration

• By inhalation of nebuliser suspension

Neonate 500 micrograms twice daily

Child 1–4 months 500 micrograms twice daily; for severe symptoms in child body-weight 2.5 kg or over, 1 mg twice daily

Budesonide (Non-proprietary) (PoM)

Dry powder for inhalation, budesonide 100 micrograms/metered inhalation, net price 200-dose unit = £8.86; 200 micrograms/metered inhalation 200-dose unit = £17.71; 400 micrograms/metered inhalation 100-dose unit = £17.71. Label: 8, counselling, administration; also 10 and steroid card with high doses

Brands include *Easyhaler*® Budesonide

Dose

Prophylaxis of asthma

• By inhalation of powder

Child 6–12 years 100–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate

asthma, 200–400 micrograms as a single dose each evening if stabilised on daily dose given in 2 divided doses

Child 12–18 years 100–800 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms (max. 800 micrograms) as a single dose each evening if stabilised on daily dose given in 2 divided doses

Budelin Novolizer® (Meda) (PoM)

Dry powder for inhalation, budesonide 200 micrograms, net price refillable inhaler device and 100-dose cartridge = £14.86; 100-dose refill cartridge = £9.59. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose

Prophylaxis of asthma

• By inhalation of powder

Child 6–12 years 200–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms as a single dose each evening if stabilised on daily dose given in 2 divided doses

Child 12–18 years 200–800 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms as a single dose each evening if stabilised on daily dose given in 2 divided doses (max. 800 micrograms)

Pulmicort® (AstraZeneca) (PoM)

Turbohaler® (= dry powder inhaler), budesonide 100 micrograms/metered inhalation, net price 200-dose unit = £11.84; 200 micrograms/metered inhalation, 100-dose unit = £11.84; 400 micrograms/metered inhalation, 50-dose unit = £13.86. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose

Prophylaxis of asthma

• By inhalation of powder

Child 5–12 years 100–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms as a single dose each evening if stabilised on daily dose given in 2 divided doses

Child 12–18 years 100–800 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms (max. 800 micrograms) as a single dose each evening if stabilised on daily dose given in 2 divided doses

Respules® (= single-dose units for nebulisation), budesonide 250 micrograms/mL, net price 20 × 2-mL (500-microgram) unit = £26.42; 500 micrograms/mL, 20 × 2-mL (1-mg) unit = £40.00. May be diluted with sterile sodium chloride 0.9%. Label: 8, counselling, administration, 10, steroid card

Note Not suitable for use in ultrasonic nebulisers

Dose

Prophylaxis of asthma

• By inhalation of nebuliser suspension

Child 3 months–12 years initially 0.5–1 mg twice daily, reduced to 250–500 micrograms twice daily

Child 12–18 years initially 1–2 mg twice daily, reduced to 0.5–1 mg twice daily

Compound preparations

For prescribing information on formoterol fumarate, see section 3.1.1.1

Symbicort® (AstraZeneca) (PoM)

Symbicort 100/6 *Turbohaler*® (= dry powder inhaler), budesonide 100 micrograms, formoterol fumarate

ate 6 micrograms/metered inhalation, net price 120-dose unit = £33.00. Label: 8, counselling, administration

Dose

Asthma, maintenance therapy

- By inhalation of powder

Child 6–12 years 1–2 puffs twice daily reduced to 1 puff once daily if control maintained

Child 12–18 years 1–2 puffs twice daily reduced to 1 puff once daily if control maintained

Asthma, maintenance and reliever therapy (but see p. 144)

- By inhalation of powder

Child 12–18 years 2 puffs daily in 1–2 divided doses; for relief of symptoms, 1 puff as needed up to max. 6 puffs at a time; max. 8 puffs daily

Symbicort 200/6 Turbohaler® (= dry powder inhaler), budesonide 200 micrograms, formoterol fumarate 6 micrograms/metered inhalation, net price 120-dose unit = £38.00. Label: 8, counselling, administration; also 10 and steroid card with high doses

Asthma, maintenance therapy

- By inhalation of powder

Child 12–18 years 1–2 puffs twice daily reduced in well-controlled asthma to 1 puff once daily

Asthma, maintenance and reliever therapy (but see p. 144)

- By inhalation of powder

Child 12–18 years 2 puffs daily in 1–2 divided doses, increased if necessary to 2 puffs twice daily; for relief of symptoms, 1 puff as needed up to max. 6 puffs at a time; max. 8 puffs daily

Symbicort 400/12 Turbohaler® (= dry powder inhaler), budesonide 400 micrograms, formoterol fumarate 12 micrograms/metered inhalation, net price 60-dose unit = £38.00. Label: 8, counselling, administration; also 10 and steroid card with high doses

Asthma, maintenance therapy

- By inhalation of powder

Child 12–18 years 1 puff twice daily; may be reduced in well-controlled asthma to 1 puff once daily

CICLESONIDE

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above; also nausea, taste disturbance

Indications and dose

Prophylaxis of asthma

- By aerosol inhalation

Child 12–18 years 160 micrograms daily as a single dose reduced to 80 micrograms daily if control maintained

Alvesco® (Takeda) (PoM)

Aerosol inhalation, ciclesonide 80 micrograms/metered inhalation, net price 120-dose unit = £32.83; 160 micrograms/metered inhalation, 60-dose unit = £19.31, 120-dose unit = £38.62. Label: 8, counselling, administration

FLUTICASONE

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above; also dyspepsia and arthralgia

Indications and dose

Prophylaxis of asthma see Management of Chronic Asthma table, p. 133, and preparations below

Flixotide® (A&H) (PoM)

Accuhaler® (dry powder for inhalation), disk containing 60 blisters of *fluticasone propionate* 50 micrograms/blister with *Accuhaler®* device, net price = £6.38; 100 micrograms/blister with *Accuhaler®* device = £8.93; 250 micrograms/blister with *Accuhaler®* device = £21.26; 500 micrograms/blister with *Accuhaler®* device = £36.14. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose

Prophylaxis of asthma

- By inhalation of powder

Child 5–16 years 50–100 micrograms twice daily adjusted as necessary; max. 200 micrograms twice daily

Child 16–18 years 100–500 micrograms twice daily, adjusted as necessary; max. 1 mg twice daily (doses above 500 micrograms twice daily initiated by a specialist)

Evohaler® (aerosol inhalation), fluticasone propionate 50 micrograms/metered inhalation, net price 120-dose unit = £5.44; 125 micrograms/metered inhalation, 120-dose unit = £21.26; 250 micrograms/metered inhalation, 120-dose unit = £36.14. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose

Prophylaxis of asthma

- By aerosol inhalation

Child 4–16 years 50–100 micrograms twice daily adjusted as necessary; max. 200 micrograms twice daily

Child 16–18 years 100–500 micrograms twice daily adjusted as necessary; max. 1 mg twice daily (doses above 500 micrograms twice daily initiated by a specialist)

Nebules® (= single-dose units for nebulisation) fluticasone propionate 250 micrograms/mL, net price 10 × 2-mL (500-microgram) unit = £9.34; 1 mg/mL, 10 × 2-mL (2-mg) unit = £37.35. May be diluted with sterile sodium chloride 0.9%. Label: 8, counselling, administration, 10, steroid card

Note Not suitable for use in ultrasonic nebulisers

Dose

Prophylaxis of asthma

- By inhalation of nebuliser suspension

Child 4–16 years 1 mg twice daily

Child 16–18 years 0.5–2 mg twice daily

Compound preparations

For prescribing information on formoterol and salmeterol, see Formoterol Fumarate, and Salmeterol, section 3.1.1.1.

Flutiform® (Napp) (PoM)

Flutiform® 50 micrograms/5 micrograms (aerosol inhalation), fluticasone propionate 50 micrograms,

formoterol fumarate 5 micrograms/metered inhalation, net price 120-dose unit = £18.00. Label: 8, counselling, administration

Dose

Prophylaxis of asthma

- By aerosol inhalation

Child 12–18 years 2 puffs twice daily

Flutiform® 125 micrograms/5 micrograms (aerosol inhalation), fluticasone propionate 125 micrograms, formoterol fumarate 5 micrograms/metered inhalation, net price 120-dose unit = £29.26. Label: 8, counselling, administration, 10, steroid card

Dose

Prophylaxis of asthma

- By aerosol inhalation

Child 12–18 years 2 puffs twice daily

Relvar Ellipta® (GSK) ▼ (PoM)

Relvar Ellipta® 92 micrograms/22 micrograms (dry powder for inhalation), fluticasone furoate 92 micrograms, vilanterol (as trifenate) 22 micrograms/inhalation (delivered dose), net price 30-dose unit = £27.80. Label: 8, counselling, administration, 10, steroid card

Cautions see notes above and also section 3.1.1.1

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—no information available

Side-effects see under Fluticasone and also section 3.1.1.1; also abdominal pain, back pain

Dose

Prophylaxis of asthma

- By inhalation of powder

Child 12–18 years 1 inhalation once daily

Important 1 inhalation (delivered dose) of fluticasone furoate 92 micrograms once daily is approximately equivalent to fluticasone propionate 250 micrograms twice daily

Relvar Ellipta® 184 micrograms/22 micrograms (dry powder for inhalation), fluticasone furoate 184 micrograms, vilanterol (as trifenate) 22 micrograms/inhalation (delivered dose), net price 30-dose unit = £38.87. Label: 8, counselling, administration, 10, steroid card

Cautions see notes above and also section 3.1.1.1

Hepatic impairment avoid in moderate to severe impairment; max. dose fluticasone furoate 92 micrograms, vilanterol 22 micrograms

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—no information available

Side-effects see under Fluticasone and also section 3.1.1.1; also abdominal pain, back pain

Dose

Prophylaxis of asthma

- By inhalation of powder

Child 12–18 years 1 inhalation once daily

Important 1 inhalation (delivered dose) of fluticasone furoate 184 micrograms once daily is approximately equivalent to fluticasone propionate 500 micrograms twice daily

Seretide® (A&H) (PoM)

Seretide 100 Accuhaler® (dry powder for inhalation), disk containing 60 blisters of fluticasone propionate 100 micrograms, salmeterol (as xinafoate) 50 micrograms/blister with *Accuhaler®* device, net price = £18.00. Label: 8, counselling, administration

Dose

Prophylaxis of asthma

- By inhalation of powder

Child 5–18 years 1 inhalation twice daily, reduced to 1 inhalation once daily if control maintained

Seretide 250 Accuhaler® (dry powder for inhalation), disk containing 60 blisters of fluticasone propionate 250 micrograms, salmeterol (as xinafoate) 50 micrograms/blister with *Accuhaler®* device, net price = £35.00. Label: 8, counselling, administration, 10, steroid card

Dose

Prophylaxis of asthma

- By inhalation of powder

Child 12–18 years 1 inhalation twice daily

Seretide 500 Accuhaler® (dry powder for inhalation), disk containing 60 blisters of fluticasone propionate 500 micrograms, salmeterol (as xinafoate) 50 micrograms/blister with *Accuhaler®* device, net price = £40.92. Label: 8, counselling, administration, 10, steroid card

Dose

Prophylaxis of asthma

- By inhalation of powder

Child 12–18 years 1 inhalation twice daily

Seretide 50 Evohaler® (aerosol inhalation), fluticasone propionate 50 micrograms, salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £18.00. Label: 8, counselling, administration

Dose

Prophylaxis of asthma

- By aerosol inhalation

Child 5–18 years 2 puffs twice daily, reduced to 2 puffs once daily if control maintained

Seretide 125 Evohaler® (aerosol inhalation), fluticasone propionate 125 micrograms, salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £35.00. Label: 8, counselling, administration, 10, steroid card

Dose

Prophylaxis of asthma

- By aerosol inhalation

Child 12–18 years 2 puffs twice daily

Seretide 250 Evohaler® (aerosol inhalation), fluticasone propionate 250 micrograms, salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £59.48. Label: 8, counselling, administration, 10, steroid card

Dose

Prophylaxis of asthma

- By aerosol inhalation

Child 12–18 years 2 puffs twice daily

MOMETASONE FUROATE

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above; also headache; less commonly dyspepsia, weight gain, palpitation

Indications and dose

Prophylaxis of asthma see also Management of Chronic Asthma table, p. 133

- By inhalation of powder

Child 12–18 years 400 micrograms as a single dose in the evening or in 2 divided doses, reduced to 200 micrograms once daily if control maintained; dose may be increased to max. 400 micrograms twice daily in severe asthma

Asmanex® (MSD) (PoM)

Twisthaler (= dry powder inhaler), mometasone furoate 200 micrograms/metered inhalation, net price 30-dose unit = £15.70, 60-dose unit = £23.54; 400 micrograms/metered inhalation, 30-dose unit = £21.78, 60-dose unit = £36.05. Label: 8, counselling, administration, 10, steroid card

Note The *Scottish Medicines Consortium* has advised (November 2003) that *Asmanex*® is restricted for use following failure of first-line inhaled corticosteroids

3.3 Cromoglicate and related therapy and leukotriene receptor antagonists

3.3.1 Cromoglicate and related therapy

3.3.2 Leukotriene receptor antagonists

3.3.1 Cromoglicate and related therapy

The mode of action of **sodium cromoglicate** and **nedocromil** is not completely understood; they may be of value as **prophylaxis** in asthma with an allergic basis, but the evidence for benefit of sodium cromoglicate in children is contentious. Prophylaxis with cromoglicate or nedocromil is less effective than with inhaled corticosteroids (see Management of Chronic Asthma table). Withdrawal of sodium cromoglicate or nedocromil should be done gradually over a period of one week—symptoms of asthma may recur.

Nedocromil may be of some benefit in the prophylaxis of exercise-induced asthma.

For the use of sodium cromoglicate and nedocromil in allergic conjunctivitis see section 11.4.2; sodium cromoglicate is used also in allergic rhinitis (section 12.2.1) and allergy-related diarrhoea (section 1.5.4).

Paradoxical bronchospasm If paradoxical bronchospasm occurs, a short-acting beta₂ agonist such as salbutamol or terbutaline (section 3.1.1.1) should be used to control symptoms; treatment with sodium cromoglicate or nedocromil should be discontinued.

Side-effects Side-effects associated with inhalation of sodium cromoglicate and nedocromil include throat irritation, cough, bronchospasm (including paradoxical bronchospasm—see above), and headache.

SODIUM CROMOGLICATE (Sodium Cromoglycate)

Cautions see notes above; also discontinue if eosinophilic pneumonia occurs

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above; also rhinitis, eosinophilic pneumonia

Indications and dose

Prophylaxis of asthma (see also Management of Chronic Asthma, p. 133)

• By aerosol inhalation

Child 5–18 years 10 mg (2 puffs) 4 times daily, increased if necessary to 6–8 times daily; an additional dose may also be taken before exercise; maintenance, 5 mg (1 puff) 4 times daily

Food allergy section 1.5.4

Allergic conjunctivitis section 11.4.2

Allergic rhinitis section 12.2.1

Intal® CFC-free inhaler (Sanofi-Aventis) (PoM)

Aerosol inhalation, sodium cromoglicate 5 mg/metered inhalation, net price 112-dose unit = £18.33. Label: 8, counselling, administration

NEDOCROMIL SODIUM

Cautions see notes above

Pregnancy see p. 131

Breast-feeding see p. 131

Side-effects see notes above; also nausea, vomiting, dyspepsia, abdominal pain, pharyngitis; rarely taste disturbances

Licensed use not licensed for use in children under 6 years

Indications and dose

Prophylaxis of asthma (but see notes above)

• By aerosol inhalation

Child 5–18 years 4 mg (2 puffs) 4 times daily, when control achieved may be possible to reduce to twice daily

Counselling Regular use is necessary

Allergic conjunctivitis section 11.4.2

Tilade® CFC-free inhaler (Sanofi-Aventis) (PoM)

Aerosol inhalation, mint-flavoured, nedocromil sodium 2 mg/metered inhalation. Net price 112-dose unit = £39.94. Label: 8, counselling, administration

3.3.2 Leukotriene receptor antagonists

The leukotriene receptor antagonists, **montelukast** and **zafirlukast**, block the effects of cysteinyl leukotrienes in the airways; they can be used in children for the management of chronic asthma with an inhaled corticosteroid or as an alternative if an inhaled corticosteroid cannot be used (see Management of Chronic Asthma table, p. 133).

Montelukast has not been shown to be more effective than a standard dose of inhaled corticosteroid, but the two drugs appear to have an additive effect. The leukotriene receptor antagonists may be of benefit in exercise-induced asthma and in those with concomitant rhinitis, but they are less effective in children with severe asthma who are also receiving high doses of other drugs.

There is some limited evidence to support the intermittent use of montelukast in children under 12 years with episodic wheeze associated with viral infections [unlicensed use]. Treatment is started at the onset of either asthma symptoms or of coryzal symptoms and continued for 7 days; there is no evidence to support this use in moderate or severe asthma.

Churg-Strauss syndrome Churg-Strauss syndrome has occurred very rarely in association with the use of leukotriene receptor antagonists; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. Prescribers

should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

Pregnancy There is limited evidence for the safe use of leukotriene receptor antagonists during pregnancy; however, they can be taken as normal in females who have shown a significant improvement in asthma not achievable with other drugs before becoming pregnant, see also p. 131.

MONTELUKAST

Cautions interactions: Appendix 1 (leukotriene receptor antagonists)

Pregnancy manufacturer advises avoid unless essential; see also notes above

Breast-feeding manufacturer advises avoid unless essential

Side-effects abdominal pain, thirst, headache, hyperkinesia (in young children); *less commonly* dry mouth, dyspepsia, oedema, dizziness, drowsiness, malaise, sleep disturbances, sleep-walking, abnormal dreams, anxiety, agitation (including aggressive behaviour or hostility), depression, psychomotor hyperactivity (including irritability and restlessness), paraesthesia, hypoaesthesia, seizures, arthralgia, myalgia (including muscle cramps), epistaxis, bruising; *rarely* palpitation, tremor, disturbance in attention, memory impairment, increased bleeding tendency; *very rarely* hepatic eosinophilic infiltration, hepatic disorders, hallucinations, suicidal thoughts and behaviour, disorientation, Churg-Strauss syndrome (see notes above), erythema nodosum, erythema multiforme

Indications and dose

Prophylaxis of asthma see notes above and Management of Chronic Asthma table, p. 133

• By mouth

Child 6 months–6 years 4 mg once daily in the evening

Child 6–15 years 5 mg once daily in the evening

Child 15–18 years 10 mg once daily in the evening

Symptomatic relief of seasonal allergic rhinitis in children with asthma

• By mouth

Child 15–18 years 10 mg once daily in the evening

Montelukast (Non-proprietary) (PoM)

Chewable tablets, montelukast (as sodium salt) 4 mg, net price 28-tab pack = £1.96; 5 mg, 28-tab pack = £2.35. Label: 23, 24

Excipients include aspartame (section 9.4.1)

Granules, montelukast (as sodium salt) 4 mg, net price 28-sachet pack = £4.01. Counselling, administration

Counselling Granules may be swallowed whole or mixed with cold, soft food (not liquid) and taken immediately

Tablets, montelukast (as sodium salt) 10 mg, net price 28-tab pack = £2.33

Singulair® (MSD) (PoM)

Chewable tablets, pink, cherry-flavoured, montelukast (as sodium salt) 4 mg, net price 28-tab pack = £25.69; 5 mg, 28-tab pack = £25.69. Label: 23, 24

Excipients include aspartame equivalent to phenylalanine 674 micrograms/4-mg tablet and 842 micrograms/5-mg tablet (section 9.4.1)

Granules, montelukast (as sodium salt) 4 mg, net price 28-sachet pack = £25.69. Counselling, administration

Counselling Granules may be swallowed whole or mixed with cold, soft food (not liquid) and taken immediately

Tablets, beige, f/c, montelukast (as sodium salt) 10 mg, net price 28-tab pack = £26.97

Note The Scottish Medicines Consortium has advised (June 2007) that *Singulair*® chewable tablets and granules are restricted for use as an alternative to low-dose inhaled corticosteroids for children 2–14 years with mild persistent asthma who have not recently had serious asthma attacks that required oral corticosteroid use, and who are not capable of using inhaled corticosteroids; *Singulair*® chewable tablets and granules should be initiated by a specialist in paediatric asthma

ZAFIRLUKAST

Cautions interactions: Appendix 1 (leukotriene receptor antagonists)

Hepatic disorders Children or their carers should be told how to recognise development of liver disorder and advised to seek medical attention if symptoms or signs such as persistent nausea, vomiting, malaise or jaundice develop

Hepatic impairment manufacturer advises avoid

Renal impairment manufacturer advises caution

Pregnancy manufacturer advises use only if potential benefit outweighs risk; see also notes above

Breast-feeding present in milk—manufacturer advises avoid

Side-effects gastro-intestinal disturbances; headache; *rarely* bleeding disorders, hypersensitivity reactions including angioedema and skin reactions, arthralgia, myalgia, hepatitis, hyperbilirubinaemia, thrombocytopenia; *very rarely* Churg-Strauss syndrome (see notes above), agranulocytosis

Indications and dose

Prophylaxis of asthma see notes above and Management of Chronic Asthma, p. 133

• By mouth

Child 12–18 years 20 mg twice daily

Accolate® (AstraZeneca) (PoM)

Tablets, f/c, zafirlukast 20 mg, net price 56-tab pack = £17.75. Label: 23

3.4 Antihistamines, immunotherapy, and allergic emergencies

3.4.1 Antihistamines

3.4.2 Allergen immunotherapy

3.4.3 Allergic emergencies

3.4.1 Antihistamines

Antihistamines (histamine H₁-receptor antagonists) are classified as *sedating* or *non-sedating*, according to their relative potential for CNS depression. Antihistamines differ in their duration of action, incidence of drowsiness, and antimuscarinic effects; the response to an antihistamine may vary from child to child (see Side-effects, p. 152). Either a sedating or a non-sedating antihistamine may be used to treat an acute allergic reaction; for conditions with more persistent symptoms which require regular treatment, a non-sedating anti-

histamine should be used to minimise the risk of sedation and psychomotor impairment associated with sedating antihistamines.

Oral antihistamines are used in the treatment of nasal allergies, particularly seasonal allergic rhinitis (hay fever), and may be of some value in vasomotor rhinitis; rhinorrhoea and sneezing is reduced, but antihistamines are usually less effective for nasal congestion. Antihistamines are used topically to treat allergic reactions in the eye (section 11.4.2) and in the nose (section 12.2.1). Topical application of antihistamines to the skin is not recommended (section 13.3).

An oral antihistamine may be used to prevent urticaria, and for the treatment of acute urticarial rashes, pruritus, insect bites, and stings. Antihistamines are also used in the management of nausea and vomiting (section 4.6), of migraine (section 4.7.4.1), and the adjunctive management of anaphylaxis and angioedema (section 3.4.3).

The *non-sedating* antihistamine **cetirizine** is safe and effective in children. Other non-sedating antihistamines that are used include **acrivastine**, **bilastine**, **desloratadine** (an active metabolite of loratadine), **fexofenadine** (an active metabolite of terfenadine), **levocetirizine** (an isomer of cetirizine), **loratadine**, **mizolastine**, and **rupatadine**. Most non-sedating antihistamines are long-acting (usually 12–24 hours). There is little evidence that desloratadine or levocetirizine confer any additional benefit—they should be reserved for children who cannot tolerate other therapies.

Sedating antihistamines are occasionally useful when insomnia is associated with urticaria and pruritus (section 4.1.1). Most of the sedating antihistamines are relatively short-acting, but promethazine may be effective for up to 12 hours. **Alimemazine** and **promethazine** have a more sedative effect than **chlorphenamine** and **cyclizine** (section 4.6). Chlorphenamine is used as an adjunct to adrenaline (epinephrine) in the emergency treatment of anaphylaxis and angioedema (section 3.4.3).

Cautions and contra-indications Antihistamines should be used with caution in children with epilepsy. Most antihistamines should be avoided in acute porphyria, but some are thought to be safe (see section 9.8.2). Sedating antihistamines have significant antimuscarinic activity—they should **not** be used in neonates and should be used with caution in children with urinary retention, glaucoma, or pyloroduodenal obstruction. Phenothiazine sedating antihistamines, such as alimemazine and promethazine, should not be given to children under 2 years, except on specialist advice, because the safety of such use has not been established. See also MHRA/CHM advice, p. 166. **Interactions:** see Appendix 1 (antihistamines).

Hepatic impairment Sedating antihistamines should be avoided in children with severe liver disease—increased risk of coma.

Pregnancy Most manufacturers of antihistamines advise avoiding their use during pregnancy; however there is no evidence of teratogenicity, except for hydroxyzine where toxicity has been reported with high doses in *animal* studies. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

Breast-feeding Most antihistamines are present in breast milk in varying amounts; although not known to

be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

Side-effects Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely in children, especially with high doses. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines (see also notes above). Side-effects that are more common with the older antihistamines include headache, psychomotor impairment, and antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances. Other rare side-effects of antihistamines include hypotension, palpitation, arrhythmias, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, hypersensitivity reactions (including bronchospasm, angioedema, anaphylaxis, rashes, and photosensitivity reactions), blood disorders, and liver dysfunction.

Non-sedating antihistamines

Skilled tasks Although drowsiness is rare, children and their carers should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

ACRIVASTINE

Cautions see notes above

Contra-indications see notes above; also hypersensitivity to triprolidine

Renal impairment avoid in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria

• By mouth

Child 12–18 years 8 mg 3 times daily

Acrivastine (Non-proprietary)

Capsules, acrivastine 8 mg, net price 12-cap pack = £2.75, 24-cap pack = £4.76. Counselling, skilled tasks

Brands include Benadryl® Allergy Relief

BILASTINE

Cautions see notes above

Contra-indications see notes above

Pregnancy avoid—limited information available; see also notes above

Breast-feeding avoid—no information available; see also notes above

Side-effects headache, malaise; *less commonly* abdominal pain, diarrhoea, increased appetite, weight gain, thirst, gastritis, prolongation of the QT interval, dyspnoea, anxiety, insomnia, vertigo, dizziness, pyrexia, oral herpes, tinnitus

Indications and dose

Symptomatic relief of allergic rhinoconjunctivitis and urticaria

- By mouth

Child 12–18 years 20 mg once daily

Counselling Advise carer and child that child should take tablet 1 hour before or 2 hours after food or fruit juice

Ilaxten® (Menarini) PoM

Tablets, scored, bilastine 20 mg, net price 30-tab pack = £15.09. Label: 23, counselling, administration

CETIRIZINE HYDROCHLORIDE

Cautions see notes above

Contra-indications see notes above

Renal impairment use half normal dose if estimated glomerular filtration rate 30–50 mL/minute/1.73m²; use half normal dose and reduce dose frequency to alternate days if estimated glomerular filtration rate 10–30 mL/minute/1.73m²; avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73m²

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 2 years

Indications and dose

Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria, atopic dermatitis

- By mouth

Child 1–2 years 250 micrograms/kg twice daily

Child 2–6 years 2.5 mg twice daily

Child 6–12 years 5 mg twice daily

Child 12–18 years 10 mg once daily

Cetirizine (Non-proprietary)

Tablets, cetirizine hydrochloride 10 mg, net price 30-tab pack = £1.06. Counselling, skilled tasks

Dental prescribing on NHS Cetirizine 10 mg Tablets may be prescribed

Oral solution, cetirizine hydrochloride 5 mg/5 mL, net price 200 mL = £1.70. Counselling, skilled tasks

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Excipients may include propylene glycol (see Excipients p. 2)

Dental prescribing on NHS Cetirizine Oral Solution 5 mg/5 mL may be prescribed

DESLOTRADINE

Note Desloratadine is a metabolite of loratadine

Cautions see notes above

Contra-indications see notes above; also hypersensitivity to loratadine

Renal impairment use with caution in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; *rarely* myalgia; *very rarely* hallucinations

Indications and dose

Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria

- By mouth

Child 1–6 years 1.25 mg once daily

Child 6–12 years 2.5 mg once daily

Child 12–18 years 5 mg once daily

Desloratadine (Non-proprietary) PoM

Tablets, desloratadine 5 mg, net price 30-tab pack = £1.35. Counselling, skilled tasks

Neoclarityn® (MSD) PoM

Tablets, f/c, desloratadine 5 mg, net price 30-tab pack = £6.77. Counselling, skilled tasks

Oral solution, sugar-free, bubblegum-flavoured, desloratadine 2.5 mg/5 mL, net price 100 mL = £6.77; 150 mL = £10.15. Counselling, skilled tasks

Excipients include propylene glycol, sorbitol 150 mg/mL (see Excipients p. 2)

FEXOFENADINE HYDROCHLORIDE

Note Fexofenadine is a metabolite of terfenadine

Cautions see notes above

Contra-indications see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

Symptomatic relief of seasonal allergic rhinitis

- By mouth

Child 6–12 years 30 mg twice daily

Child 12–18 years 120 mg once daily

Symptomatic relief of chronic idiopathic urticaria

- By mouth

Child 12–18 years 180 mg once daily

Fexofenadine Hydrochloride (Non-proprietary) PoM

Tablets, f/c, fexofenadine hydrochloride 120 mg, net price 30-tab pack = £2.85; 180 mg, 30-tab pack = £3.70. Label: 5, counselling, skilled tasks

Telfast® (Sanofi-Aventis) PoM

Tablets, f/c, peach, fexofenadine hydrochloride 30 mg, net price 60-tab pack = £5.46; 120 mg, 30-tab pack = £5.99; 180 mg, 30-tab pack = £7.58. Label: 5, counselling, skilled tasks

LEVOCETIRIZINE HYDROCHLORIDE

Note Levocetirizine is an isomer of cetirizine

Cautions see notes above

Contra-indications see notes above

Renal impairment estimated glomerular filtration rate 30–50 mL/minute/1.73 m², reduce dose frequency to alternate days; estimated glomerular filtration rate 10–30 mL/minute/1.73 m², reduce dose frequency to every 3 days; estimated glomerular filtration rate less than 10 mL/minute/1.73 m², avoid

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; *very rarely* weight gain

Licensed use tablets not licensed for use in children under 6 years

Indications and dose

Symptomatic relief of allergy such as hay fever, urticaria

- **By mouth**

Child 2–6 years 1.25 mg twice daily

Child 6–18 years 5 mg once daily

Levocetirizine Hydrochloride (Non-proprietary) (PoM)

Tablets, levocetirizine hydrochloride 5 mg, net price 30-tab pack = £3.93. Counselling, skilled tasks

Xyzal® (UCB Pharma) (PoM)

Tablets, f/c, levocetirizine hydrochloride 5 mg, net price 30-tab pack = £4.39. Counselling, skilled tasks

Oral solution, sugar-free, levocetirizine hydrochloride 2.5 mg/5 mL, net price 200 mL = £6.00. Counselling, skilled tasks

LORATADINE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment reduce dose frequency to alternate days in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria

- **By mouth**

Child 2–12 years

Body-weight under 30 kg 5 mg once daily

Body-weight over 30 kg 10 mg once daily

Child 12–18 years 10 mg once daily

Loratadine (Non-proprietary)

Tablets, loratadine 10 mg, net price 30-tab pack = £1.00. Counselling, skilled tasks

Dental Prescribing on NHS Loratadine 10 mg Tablets may be prescribed

Syrup, loratadine 5 mg/5 mL, net price 100 mL = £2.19. Counselling, skilled tasks

Excipients may include propylene glycol (see Excipients, p. 2)

Dental Prescribing on NHS Loratadine Syrup 5 mg/5 mL may be prescribed

MIZOLASTINE

Cautions see notes above

Contra-indications see notes above; also susceptibility to QT-interval prolongation (including cardiac disease and hypokalaemia)

Hepatic impairment manufacturer recommends avoid in significant impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; weight gain; anxiety, asthenia; *less commonly* arthralgia and myalgia

Indications and dose

Symptomatic relief of allergy such as hay fever, urticaria

- **By mouth**

Child 12–18 years 10 mg once daily

Mizollen® (Sanofi-Aventis) (PoM)

Tablets, m/r, scored, mizolastine 10 mg, net price 30-tab pack = £6.92. Label: 25, counselling, skilled tasks

RUPATADINE

Cautions see notes above; also susceptibility to QT-interval prolongation (including cardiac disease and hypokalaemia)

Hepatic impairment manufacturer advises avoid—no information available

Renal impairment manufacturer advises avoid—no information available

Pregnancy manufacturer advises caution—limited information available; see also notes above

Breast-feeding manufacturer advises caution; see also notes above

Side-effects see notes above; also asthenia; *less commonly* pyrexia, irritability, increased appetite, arthralgia, and myalgia

Indications and dose

Symptomatic relief of allergic rhinitis and urticaria

- **By mouth**

Child 12–18 years 10 mg once daily

Rupafin® (GSK) ▼ (PoM)

Tablets, salmon, rupatadine (as fumarate) 10 mg, net price 30-tab pack = £5.00. Counselling, skilled tasks

Sedating antihistamines

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

ALIMEMAZINE TARTRATE

(Trimeprazine tartrate)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment avoid

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 2 years

Indications and dose

Urticaria, pruritus

- **By mouth**

Child 6 months–2 years 250 micrograms/kg (max. 2.5 mg) 3–4 times daily—specialist use only

Child 2–5 years 2.5 mg 3–4 times daily

Child 5–12 years 5 mg 3–4 times daily

Child 12–18 years 10 mg 2–3 times daily, in severe cases up to max. 100 mg daily

Premedication section 15.1.4

- **By mouth**

Child 2–7 years up to max. 2 mg/kg 1–2 hours before operation

Alimemazine (Non-proprietary) (PoM)

Tablets, alimemazine tartrate 10 mg, net price 28-tab pack = £6.00. Label: 2

Oral Solution, alimemazine tartrate 7.5 mg/5 mL, net price 100 mL = £13.80; 30 mg/5 mL, 100-mL = £40.24. Label: 2

CHLORPHENAMINE MALEATE

(Chlorpheniramine maleate)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also exfoliative dermatitis and tinnitus reported; injections may cause transient hypotension or CNS stimulation and may be irritant

Licensed use *syrup* not licensed for use in children under 1 year; *tablets* not licensed for use in children under 6 years; *injection* not licensed for use in neonates

Indications and dose

Symptomatic relief of allergy such as hay fever, urticaria, food allergy, drug reactions, relief of itch associated with chickenpox

- By mouth

Child 1 month–2 years 1 mg twice daily

Child 2–6 years 1 mg every 4–6 hours, max. 6 mg daily

Child 6–12 years 2 mg every 4–6 hours, max. 12 mg daily

Child 12–18 years 4 mg every 4–6 hours, max. 24 mg daily

Emergency treatment of anaphylactic reactions, symptomatic relief of allergy

- By intramuscular or intravenous injection

Child under 6 months 250 micrograms/kg (max. 2.5 mg), repeated if required up to 4 times in 24 hours

Child 6 months–6 years 2.5 mg, repeated if required up to 4 times in 24 hours

Child 6–12 years 5 mg, repeated if required up to 4 times in 24 hours

Child 12–18 years 10 mg, repeated if required up to 4 times in 24 hours

Administration for *intravenous injection*, give over 1 minute; if small dose required, dilute with Sodium Chloride 0.9%

Chlorphenamine (Non-proprietary)

Tablets, chlorphenamine maleate 4 mg, net price 28 = 90p. Label: 2

Dental prescribing on NHS Chlorphenamine tablets may be prescribed

Oral solution, chlorphenamine maleate 2 mg/5 mL, net price 150 mL = £2.51. Label: 2

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Chlorphenamine oral solution may be prescribed

Injection (PoM)¹, chlorphenamine maleate 10 mg/mL, net price 1-mL amp = £2.80

1. (PoM) restriction does not apply where administration is for saving life in emergency

Piriton® (GSK Consumer Healthcare)

Tablets, yellow, scored, chlorphenamine maleate 4 mg, net price 28 = £1.62. Label: 2

Syrup, chlorphenamine maleate 2 mg/5 mL, net price 150 mL = £2.49. Label: 2

HYDROXYZINE HYDROCHLORIDE

Cautions see notes above; also susceptibility to QT-interval prolongation

Contra-indications see notes above

Hepatic impairment reduce daily dose by one-third; see also notes above

Renal impairment reduce daily dose by half

Pregnancy toxicity in *animal* studies with high doses; see also notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use *Ucerax*® syrup not licensed for use in children under 1 year

Indications and dose**Pruritus**

- By mouth

Child 6 months–6 years initially 5–15 mg at night, increased if necessary to 50 mg daily in 3–4 divided doses

Child 6–12 years initially 15–25 mg at night, increased if necessary to 50–100 mg daily in 3–4 divided doses

Child 12–18 years initially 25 mg at night, increased if necessary to 100 mg in 3–4 divided doses

Atarax® (Alliance) (PoM)

Tablets, both f/c, hydroxyzine hydrochloride 10 mg (orange), net price 84-tab pack = £2.18; 25 mg (green), 28-tab pack = £1.22. Label: 2

Ucerax® (UCB Pharma) (PoM)

Tablets ~~and~~ f/c, scored, hydroxyzine hydrochloride 25 mg, net price 25-tab pack = £1.22. Label: 2

Syrup, hydroxyzine hydrochloride 10 mg/5 mL. Net price 200-mL pack = £1.78. Label: 2

KETOTIFEN

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also irritability, nervousness; *less commonly* cystitis; *rarely* weight gain; *very rarely* Stevens-Johnson syndrome

Indications and dose

Symptomatic relief of allergy such as allergic rhinitis

- By mouth

Child 3–18 years 1 mg twice daily

Zaditen® (Swedish Orphan) (PoM)

Tablets, scored, ketotifen (as hydrogen fumarate) 1 mg, net price 60-tab pack = £7.53. Label: 2, 21

Elixir, ketotifen (as hydrogen fumarate), 1 mg/5 mL, net price 300 mL (strawberry-flavoured) = £8.91. Label: 2, 21

PROMETHAZINE HYDROCHLORIDE

Cautions see notes above; also severe coronary artery disease

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment use with caution

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also restlessness

Indications and dose

Symptomatic relief of allergy such as hay fever, insomnia associated with urticaria and pruritus

- By mouth

Child 2–5 years 5 mg twice daily or 5–15 mg at night

Child 5–10 years 5–10 mg twice daily or 10–25 mg at night

Child 10–18 years 10–20 mg 2–3 times daily or 25 mg at night increased to 25 mg twice daily if necessary

Sedation section 4.1.1

Nausea and vomiting section 4.6

Phenergan® (Sanofi-Aventis)

Tablets, both blue, f/c, promethazine hydrochloride 10 mg, net price 56-tab pack = £2.96; 25 mg, 56-tab pack = £4.65. Label: 2

Dental prescribing on NHS May be prescribed as Promethazine Hydrochloride Tablets 10 mg or 25 mg

Elixir, golden, promethazine hydrochloride 5 mg/5 mL. Net price 100 mL = £2.85. Label: 2

Excipients include sulfites

Electrolytes Na⁺ 1.6 mmol/5 mL

Dental prescribing on NHS May be prescribed as Promethazine Hydrochloride Oral Solution 5 mg/5 mL

sensitivity reaction occurs), or ACE inhibitors (risk of severe anaphylactoid reactions).

Hypersensitivity reactions to immunotherapy (especially to wasp and bee venom extracts) can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore, facilities for cardiopulmonary resuscitation must be immediately available and the child needs to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), **even when mild**, the child should be observed until these have **resolved completely**. The first dose of oral grass pollen extract (*Grazax*®) should be taken under medical supervision and the child should be monitored for 20–30 minutes.

For details on the management of anaphylaxis, see section 3.4.3.

Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

NICE guidance

Pharmalgen® for bee and wasp venom allergy (February 2012)

Pharmalgen® is an option for the treatment of IgE-mediated bee and wasp venom allergy in those who have had:

- a severe systemic reaction to bee or wasp venom;
- a moderate systemic reaction to bee or wasp venom and who have a raised baseline serum-tryptase concentration, a high risk of future stings, or anxiety about future stings.

Treatment with *Pharmalgen*® should be initiated and monitored in a specialist centre experienced in venom immunotherapy.

www.nice.org.uk/TA246

3.4.2 Allergen immunotherapy

Immunotherapy using allergen vaccines containing house dust mite, animal dander (cat or dog), or extracts of grass and tree pollen can improve symptoms of asthma and allergic rhino-conjunctivitis in children. A vaccine containing extracts of wasp and bee venom is used to reduce the risk of severe anaphylaxis and systemic reactions in children with hypersensitivity to wasp and bee stings. An oral preparation of grass pollen extract (*Grazax*®) is also licensed for disease-modifying treatment of grass pollen induced rhinitis and conjunctivitis. Children requiring immunotherapy must be referred to a hospital specialist for accurate allergy diagnosis, assessment, and treatment.

Desensitising vaccines

In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:

- seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergic drugs;
- hypersensitivity to wasp and bee venoms.

Desensitising vaccines should generally be avoided or used with particular care in children with asthma.

Desensitising vaccines should be avoided in pregnant women, in children under 5 years, and in those taking beta-blockers (adrenaline will be ineffective if a hyper-

BEE AND WASP ALLERGEN EXTRACTS

Cautions see notes above and consult product literature

Contra-indications see notes above and consult product literature

Pregnancy avoid

Side-effects consult product literature

Indications and dose

Hypersensitivity to wasp or bee venom (see notes above)

- By subcutaneous injection

Consult product literature

Pharmalgen® (ALK-Abellö) [Pm]

Bee venom extract (*Apis mellifera*) or wasp venom extract (*Vespula* spp.). Net price initial treatment set = £65.77 (bee), £80.64 (wasp); maintenance treatment set = £76.51 (bee), £98.44 (wasp)

GRASS AND TREE POLLEN EXTRACTS

Cautions see notes above and consult product literature

Contra-indications see notes above and consult product literature

Pregnancy consult product literature

Side-effects consult product literature

Indications and dose

Treatment of seasonal allergic hay fever due to grass or tree pollen (see notes above)

See under preparations, below

Pollinex® (Allergy) (PoM)

Grasses and rye or tree pollen extract, net price initial treatment set (3 vials) and extension course treatment (1 vial) = £450.00

Dose

- By subcutaneous injection

Consult product literature

Grass pollen extract

Grazax® (ALK-Abellö) (PoM)

Oral lyophilisates (= freeze-dried tablets), grass pollen extract 75 000 units, net price 30-tab pack = £80.12. Counselling, administration

Dose

- By mouth

Child 5–18 years 1 tablet daily; start treatment at least 4 months before start of pollen season and continue for up to 3 years

Counselling Tablets should be placed under the tongue and allowed to disperse. Advise carer and child that child not to swallow for 1 minute, or eat or drink for 5 minutes, after taking the tablet

NICE guidance

Omalizumab for severe persistent allergic asthma (April 2013)

Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in children aged 6 years and over

- who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and
- only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.

Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta₂ agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

Children currently receiving omalizumab whose disease does not meet the criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA278

Omalizumab

Omalizumab is a monoclonal antibody that binds to immunoglobulin E (IgE). It is licensed for use as additional therapy in children over 6 years with proven IgE-mediated sensitivity to inhaled allergens, whose severe persistent allergic asthma cannot be controlled adequately with high-dose inhaled corticosteroid together with a long-acting beta₂ agonist. Omalizumab should be initiated by physicians experienced in the treatment of severe persistent asthma.

Churg-Strauss syndrome has occurred rarely in patients given omalizumab; the reaction is usually associated with the reduction or withdrawal of oral corticosteroid therapy. Churg-Strauss syndrome can present as eosinophilia, vasculitic rash, cardiac complications, worsening pulmonary symptoms, or peripheral neuropathy. Hypersensitivity reactions can also occur immediately following treatment with omalizumab or sometimes more than 24 hours after the first injection.

For details on the management of anaphylaxis, see section 3.4.3.

The *Scottish Medicines Consortium*, p. 3 has advised (May 2011) that omalizumab is accepted for restricted use within NHS Scotland as add-on therapy to improve asthma control in children (6 to 12 years), adolescents, and adults with severe persistent allergic asthma. Omalizumab is restricted to patients who are prescribed chronic systemic corticosteroids and in whom all other treatments have failed. The response should be assessed at 16 weeks and omalizumab treatment discontinued in patients who have not shown a marked improvement in overall asthma control.

OMALIZUMAB

Cautions autoimmune disease; susceptibility to helminth infections—discontinue if infection does not respond to anthelmintic

Hepatic impairment manufacturer advises caution—no information available

Renal impairment manufacturer advises caution—no information available

Pregnancy manufacturer advises avoid unless essential; no evidence of teratogenicity in *animal* studies

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects abdominal pain, headache, pyrexia; *less commonly* dyspepsia, nausea, diarrhoea, weight gain, postural hypotension, flushing, pharyngitis, bronchospasm, cough, syncope, paraesthesia, dizziness, drowsiness, malaise, influenza-like illness, photosensitivity, urticaria, rash, pruritus; *rarely* laryngedema, parasitic infection, antibody formation; *also reported* arterial thromboembolic events, Churg-Strauss syndrome (see notes above), thrombocytopenia, arthralgia, myalgia, joint swelling, alopecia, serum sickness (including fever and lymphadenopathy)

Indications and dose

Prophylaxis of severe persistent allergic asthma (see notes above)

- By subcutaneous injection

Child 6–18 years according to immunoglobulin E concentration and body-weight, consult product literature

Xolair® (Novartis) (PoM)

Injection, omalizumab 150 mg/mL, net price 0.5-mL (75-mg) prefilled syringe = £128.07; 1-mL (150-mg) prefilled syringe = £256.15

3.4.3 Allergic emergencies

Adrenaline (epinephrine) provides physiological reversal of the immediate symptoms associated with hypersensitivity reactions such as *anaphylaxis* and *angioedema*.

Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by the rapid onset of respiratory and/or circulatory problems and is usually associated with skin and mucosal changes; prompt treatment is required. Children with pre-existing asthma, especially poorly controlled asthma, are at particular risk of life-threatening reactions. Insect stings are a recognised risk (in particular wasp and bee stings). Latex and certain foods, including eggs, fish, cows' milk protein, peanuts, sesame, shellfish, soy, and tree nuts may also precipitate anaphylaxis. Medicinal products particularly associated with anaphylaxis include blood products, vaccines, allergen immunotherapy preparations, antibacterials, aspirin and other NSAIDs, and neuromuscular blocking drugs. In the case of drugs, anaphylaxis is more likely after parenteral administration; resuscitation facilities must always be available when giving injections associated with special risk. Refined arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergens.

Treatment of anaphylaxis

First-line treatment includes:

- securing the airway, restoration of blood pressure (laying the child flat and raising the legs, or in the recovery position if unconscious or nauseous and at risk of vomiting);
- administering **adrenaline (epinephrine)** by **intramuscular** injection (for doses see Intramuscular Adrenaline, below); the dose should be repeated if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function [important: possible need for *intravenous route using dilute solution* (Adrenaline 1 in 10 000), see Intravenous Adrenaline below];
- administering high-flow **oxygen** (section 3.6) and **intravenous fluids** (section 9.2.2);
- administering an antihistamine, such as **chlorphenamine**, (section 3.4.1) by slow intravenous injection or intramuscular injection as adjunctive treatment given after adrenaline. An intravenous corticosteroid (section 6.3.2) such as **hydrocortisone** (preferably as sodium succinate) is of secondary value in the initial management of anaphylaxis because the onset of action is delayed for several hours, but should be given to prevent further deterioration in severely affected children.

Continuing respiratory deterioration requires further treatment with **bronchodilators** including inhaled or intravenous salbutamol (see p. 137), inhaled ipratropium (see p. 140), intravenous aminophylline (see p. 141), or intravenous magnesium sulfate [unlicensed indication] (see Management of Acute Asthma, p. 132). In addition to oxygen, assisted respiration and possibly emergency tracheotomy may be necessary.

When a child is so ill that there is doubt as to the adequacy of the circulation, the initial injection of adrenaline may need to be given as a *dilute solution by the intravenous route*, or by the intrathecal route if venous access is difficult—for details of cautions, dose and strength, see under Intravenous Adrenaline (Epinephrine), below.

On discharge, the child should be considered for further treatment with an oral antihistamine (section 3.4.1) and an oral corticosteroid (section 6.3.2) for up to 3 days to reduce the risk of further reaction. The child, or carer, should be instructed to return to hospital if symptoms recur and to contact their general practitioner for follow-up.

Children who are suspected of having had an anaphylactic reaction should be referred to a specialist for specific allergy diagnosis. Avoidance of the allergen is the principal treatment; if appropriate, an adrenaline auto-injector should be given or a replacement supplied (see Self-administration of Adrenaline, p. 159).

Intramuscular adrenaline (epinephrine)

The *intramuscular route* is the *first choice route* for the administration of adrenaline in the management of anaphylaxis. Adrenaline is best given as an intramuscular injection into the anterolateral aspect of the middle third of the thigh, it has a rapid onset of action after intramuscular administration and in the shocked patient its absorption from the intramuscular site is faster and more reliable than from the subcutaneous site.

Children with severe allergy, and their carers, should ideally be instructed in the self-administration of adrenaline by intramuscular injection (for details see Self-administration of Adrenaline (Epinephrine), p. 159).

Prompt injection of adrenaline is of paramount importance. The following adrenaline doses are recommended for the emergency treatment of anaphylaxis by appropriately trained healthcare professionals, and are based on the revised recommendations of the Working Group of the Resuscitation Council (UK).

Dose of intramuscular injection of adrenaline (epinephrine) for the emergency treatment of anaphylaxis by healthcare professionals

Age range	Dose	Volume of adrenaline 1 in 1000 (1 mg/mL)
Under 6 years	150 micrograms	0.15 mL ¹
6–12 years	300 micrograms	0.3 mL
12–18 years	500 micrograms	0.5 mL ²
These doses may be repeated several times if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function.		

1. Use suitable syringe for measuring small volume
2. 300 micrograms (0.3 mL) if child is small or prepubertal

Intravenous adrenaline (epinephrine)

Intravenous adrenaline should be given only by those experienced in its use, in a setting where patients can be carefully monitored.

Where the child is severely ill and there is real doubt about adequacy of the circulation and absorption from the intramuscular injection site, adrenaline may be given by **slow intravenous injection**. Children may respond to as little as 1 microgram/kg (0.01 mL/kg) of the dilute 1 in 10 000 adrenaline injection by **slow intravenous injection** repeated according to response. A single dose of adrenaline by intravenous injection should not exceed 50 micrograms; if multiple doses are required consider giving adrenaline by slow intravenous infusion. Great vigilance is needed to ensure that the *correct strength* of adrenaline injection is used; anaphylactic shock kits need to make a *very clear distinction* between the 1 in 10 000 strength and the 1 in 1000 strength. It is also important that, where intramuscular injection might still succeed, time should not be wasted seeking intravenous access.

For reference to the use of the intravenous route for *acute hypotension*, see section 2.7.2.

Self-administration of adrenaline (epinephrine)

Children at considerable risk of anaphylaxis need to carry (or have available) adrenaline at all times and the child, or child's carers, need to be *instructed in advance* when and how to inject it. Packs for self-administration need to be **clearly labelled with instructions** on how to administer adrenaline (intramuscularly, preferably at the midpoint of the outer thigh, through light clothing if necessary). It is important to ensure that an adequate supply is provided to treat symptoms until medical assistance is available.

Adrenaline for administration by intramuscular injection is available in 'auto-injectors' (e.g. *Emerade*®, *EpiPen*®, or *Jext*®), pre-assembled syringes fitted with a needle suitable for very rapid administration (if necessary by a bystander or a healthcare provider if it is the only preparation available); injection technique is device specific.

For doses of adrenaline for self-administration, see individual preparations under Adrenaline/Epinephrine (Intramuscular Injection for Self-Administration, above).

ADRENALINE/EPINEPHRINE

Cautions for cautions in non-life-threatening situations, see section 2.7.2

Interactions Severe anaphylaxis in children taking beta-blockers may not respond to adrenaline—consider bronchodilator therapy, see intravenous salbutamol (section 3.1.1.1); furthermore, adrenaline may cause severe hypertension and bradycardia in those receiving non-cardioselective beta-blockers. Other **interactions**, see Appendix 1 (sympathomimetics).

Renal impairment section 2.7.2

Pregnancy section 2.7.2

Breast-feeding section 2.7.2

Side-effects section 2.7.2

Licensed use auto-injector delivering 150-microgram dose of adrenaline not licensed for use in children body-weight under 15 kg

Indications and dose

Acute anaphylaxis

- By intramuscular injection (preferably midpoint in anterolateral thigh) of 1 in 1000 (1 mg/mL) solution for administration by *healthcare professionals*

See notes and table above

- By intramuscular injection for *self-administration*

See under preparations

Acute anaphylaxis when there is doubt as to the adequacy of the circulation

- By slow intravenous injection of 1 in 10 000 (100 micrograms/mL) solution (extreme caution—specialist use only)

See notes above

Safe Practice

Intravenous route should be used with **extreme care** by specialists only, see notes above

Croup (section 3.1)

- By inhalation of nebulised solution of adrenaline 1 in 1000 (1 mg/mL)

Child 1 month–12 years 400 micrograms/kg (max. 5 mg), repeated after 30 minutes if necessary

Administration For nebulisation, dilute adrenaline 1 in 1000 solution with sterile sodium chloride 0.9% solution

Acute hypotension, low cardiac output section 2.7.2

Cardiopulmonary resuscitation section 2.7.3

Intramuscular or subcutaneous

¹Adrenaline/Epinephrine 1 in 1000 (Non-proprietary) (PoM)

Injection, adrenaline (as acid tartrate) 1 mg/mL, net price 0.5-mL amp = £4.72; 1-mL amp = 39p

Excipients may include sulfites

¹Minijet® Adrenaline 1 in 1000 (UCB Pharma) (PoM)

Injection, adrenaline (as hydrochloride) 1 in 1000 (1 mg/mL). Net price 1 mL (with 25 gauge × 0.25 inch needle for subcutaneous injection) = £13.90, 1 mL (with 21 gauge × 1.5 inch needle for intramuscular injection) = £15.00 (both disposable syringes)

Excipients include sulfites

Intravenous

Extreme caution, see notes above

Adrenaline/Epinephrine 1 in 10 000, Dilute (Non-proprietary) (PoM)

Injection, adrenaline (as acid tartrate) 100 micrograms/mL, 10-mL amp, 1-mL and 10-mL prefilled syringe

Excipients may include sulfites

¹Minijet® Adrenaline 1 in 10 000 (UCB Pharma) (PoM)

Injection, adrenaline (as hydrochloride) 1 in 10 000 (100 micrograms/mL), net price 3-mL prefilled syringe = £7.54; 10-mL prefilled syringe = £6.99

Excipients include sulfites

1. (PoM) restriction does not apply to the intramuscular administration of up to 1 mg of adrenaline injection 1 in 1000 (1 mg/mL) for the emergency treatment of anaphylaxis

■ Intramuscular injection for self-administration

Note Injection technique is device specific. To ensure patients receive the auto-injector device that they have been trained to use, prescribers should specify the brand to be dispensed.

Emerade® (iMed) (PoM)

¹Emerade® 150 micrograms, (delivering a single dose of adrenaline (as tartrate) 150 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 0.5-mL auto-injector device = £26.94.

Excipients include sulfites

Note 0.35 mL of the solution remains in the auto-injector device after use

Dose

Acute anaphylaxis

- By intramuscular injection

Child body-weight under 15 kg 150 micrograms repeated after 5–15 minutes as necessary

Child body-weight 15–30 kg 150 micrograms (but on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children) repeated after 5–15 minutes as necessary

¹Emerade® 300 micrograms, (delivering a single dose of adrenaline (as tartrate) 300 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 0.5-mL auto-injector device = £26.94

Excipients include sulfites

Note 0.2 mL of the solution remains in the auto-injector device after use

Dose

Acute anaphylaxis

- By intramuscular injection

Child body-weight over 30 kg 300 micrograms repeated after 5–15 minutes as necessary

¹Emerade® 500 micrograms, (delivering a single dose of adrenaline (as tartrate) 500 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 0.5-mL auto-injector device = £28.74

Excipients include sulfites

Note No solution remains in the auto-injector device after use

Dose

Acute anaphylaxis

- By intramuscular injection

Child 12–18 years at risk of severe anaphylaxis
500 micrograms repeated after 5–15 minutes as necessary

EpiPen® (Meda) (PoM)

EpiPen® Jr Auto-injector 0.15 mg (delivering a single dose of adrenaline 150 micrograms), adrenaline 500 micrograms/mL (1 in 2000), net price 2-mL auto-injector device = £26.45, 2 × 2-mL auto-injector device = £52.90

Excipients include sulfites

Note 1.7 mL of the solution remains in the auto-injector device after use

Dose

Acute anaphylaxis

- By intramuscular injection

Child body-weight under 15 kg 150 micrograms repeated after 5–15 minutes as necessary

Child body-weight 15–30 kg 150 micrograms (but on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children) repeated after 5–15 minutes as necessary

1. (PoM) restriction does not apply to the intramuscular administration of up to 1 mg of adrenaline injection 1 in 1000 (1 mg/mL) for the emergency treatment of anaphylaxis

¹EpiPen® Auto-injector 0.3 mg (delivering a single dose of adrenaline 300 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 2-mL auto-injector device = £26.45, 2 × 2-mL auto-injector device = £52.90

Excipients include sulfites

Note 1.7 mL of the solution remains in the auto-injector device after use

Dose

Acute anaphylaxis

- By intramuscular injection

Child body-weight over 30 kg 300 micrograms repeated after 5–15 minutes as necessary

Jext® (ALK-Abelló) (PoM)

¹Jext® 150 micrograms (delivering a single dose of adrenaline (as tartrate) 150 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 1.4-mL auto-injector device = £23.99

Excipients include sulfites

Note 1.25 mL of the solution remains in the auto-injector device after use

Dose

Acute anaphylaxis

- By intramuscular injection

Child body-weight under 15 kg 150 micrograms repeated after 5–15 minutes as necessary

Child body-weight 15–30 kg 150 micrograms (but on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children) repeated after 5–15 minutes as necessary

¹Jext® 300 micrograms (delivering a single dose of adrenaline (as tartrate) 300 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 1.4-mL auto-injector device = £23.99

Excipients include sulfites

Note 1.1 mL of the solution remains in the auto-injector device after use

Dose

Acute anaphylaxis

- By intramuscular injection

Child body-weight over 30 kg 300 micrograms repeated after 5–15 minutes as necessary

Angioedema

Angioedema is dangerous if *laryngeal oedema* is present. In this circumstance adrenaline (epinephrine) injection and oxygen should be given as described under Anaphylaxis (see above); antihistamines and corticosteroids should also be given (see again above). Tracheal intubation may be necessary. In some children with laryngeal oedema, adrenaline 1 in 1000 (1 mg/mL) solution may be given by nebuliser. However, nebulised adrenaline cannot be relied upon for a systemic effect—intramuscular adrenaline should be used.

Hereditary angioedema The treatment of hereditary angioedema should be under specialist supervision. Unlike allergic angioedema, adrenaline, corticosteroids, and antihistamines should not be used for the treatment of acute attacks, including attacks involving laryngeal oedema, as they are ineffective and may delay appropriate treatment—intubation may be necessary. The administration of **C1-esterase inhibitor** (in fresh frozen plasma or in partially purified form) can terminate acute attacks of *hereditary angioedema*; it can also be used for short-term prophylaxis before dental, medical, or surgical procedures. **Tranexamic acid** (section 2.11) is used for short-term or long-

term prophylaxis of hereditary angioedema; short-term prophylaxis is started several days before planned procedures which may trigger an acute attack of hereditary angioedema (e.g. dental work) and continued for 2–5 days afterwards. **Danazol** [unlicensed indication, see BNF section 6.7.2] is best avoided in children because of its androgenic effects, but it can be used for short-term prophylaxis of hereditary angioedema.

C1-ESTERASE INHIBITOR

C1-esterase inhibitor is prepared from human plasma

Cautions vaccination against hepatitis A (p. 612) and hepatitis B (p. 614) may be required

Pregnancy manufacturer advises avoid unless essential

Side-effects thrombosis (with high doses), headache, fever

Indications and dose

See preparations

Beriner[®] (CSL Behring) [PoM]

Injection, powder for reconstitution, C1-esterase inhibitor, net price 500-unit vial (with solvent) = £467.50

Electrolytes Na⁺ approx. 2.1 mmol/vial

Dose

Acute attacks of hereditary angioedema (specialist use only)

- By slow intravenous injection or intravenous infusion
Child 1 month–18 years 20 units/kg

Short-term prophylaxis of hereditary angioedema before dental, medical, or surgical procedures (specialist use only)

- By slow intravenous injection or intravenous infusion
Child 1 month–18 years 15–30 units/kg (max. 1000 units) as a single dose less than 6 hours before procedure

Cinryze[®] (ViroPharma) ▼ [PoM]

Injection, powder for reconstitution, C1-esterase inhibitor, net price 500-unit vial (with solvent) = £668.00.

Electrolytes Na⁺ approx. 0.5 mmol/vial

Dose

Acute attacks of hereditary angioedema (specialist use only)

- By slow intravenous injection
Child 12–18 years 1000 units as a single dose; dose may be repeated if necessary

Short-term prophylaxis of hereditary angioedema before dental, medical, or surgical procedures (specialist use only)

- By slow intravenous injection
Child 12–18 years 1000 units up to 24 hours before procedure

Long-term prophylaxis of severe, recurrent attacks of hereditary angioedema where acute treatment is inadequate, or when oral prophylaxis is inadequate or not tolerated (specialist use only)

- By slow intravenous injection
Child 12–18 years 1000 units every 3–4 days, interval between doses adjusted according to response

Administration for slow intravenous injection, reconstitute (with solvent provided) to a concentration of 100 units/mL; give at a rate of 1 mL/minute

3.5 Respiratory stimulants and pulmonary surfactants

3.5.1 Respiratory stimulants

3.5.2 Pulmonary surfactants

3.5.1 Respiratory stimulants

Respiratory stimulants (analeptic drugs), such as caffeine, reduce the frequency of neonatal apnoea, and the need for mechanical ventilation during the first 7 days of treatment. They are typically used in the management of very preterm neonates, and continued until a corrected gestational age of 34 to 35 weeks is reached (or longer if necessary). They should only be given under expert supervision in hospital; it is important to rule out any underlying disorder, such as seizures, hypoglycaemia, or infection, causing respiratory exhaustion before starting treatment with a respiratory stimulant.

Caffeine citrate is licensed for the treatment of apnoea in preterm neonates. It is well absorbed when given orally. The therapeutic range for plasma-caffeine concentration is usually 10–20 mg/litre (50–100 micromol/litre), but a concentration of 25–35 mg/litre (130–180 micromol/litre) may be required.

Safe practice

From August 2013, all licensed preparations of caffeine are required to be labelled as caffeine citrate. To minimise the risk of dosing errors, **always state dose in terms of caffeine citrate when prescribing caffeine.**

Caffeine citrate 2 mg \equiv caffeine base 1 mg

CAFFEINE CITRATE

Cautions gastro-oesophageal reflux; cardiovascular disease; monitor for recurrence of apnoea for 1 week after stopping treatment; **interactions:** Appendix 1 (caffeine citrate)

Side-effects hypertension, tachycardia, irritability, restlessness, hypoglycaemia, hyperglycaemia, fluid and electrolyte imbalance; *also reported* gastro-oesophageal reflux

Indications and dose

Neonatal apnoea

- By mouth or by intravenous infusion

Neonate initially 20 mg/kg either by intravenous infusion over 30 minutes or by mouth, then 5 mg/kg once daily either by intravenous infusion over 10 minutes or by mouth, starting 24 hours after the initial dose; dose may be increased to 10 mg/kg daily if necessary

Safe practice

When prescribing, always state dose in terms of caffeine citrate

Caffeine citrate 2 mg \equiv caffeine base 1 mg

Administration caffeine citrate injection may be administered by mouth or by intravenous infusion

Caffeine citrate (Non-proprietary) (PoM)

Injection, caffeine citrate 10 mg/mL, net price 1-mL amp = £4.89

Note Some stock packaged as caffeine base

Oral solution, caffeine citrate 10 mg/mL, net price 5-mL vial = £24.41

Note Some stock packaged as caffeine base

Peyona® (Chiesi) (PoM)

Injection and oral solution, caffeine citrate 20 mg/mL, net price 1-mL amp = £17.25

Note The *Scottish Medicines Consortium*, p. 3 has advised (September 2013) that *Peyona*® is accepted for use within NHS Scotland for the treatment of primary apnoea of premature newborns only whilst *Peyona*® is available at the price agreed in the patient access scheme

3.5.2 Pulmonary surfactants

Pulmonary surfactants derived from animal lungs, **beractant** and **poractant alfa** are used to prevent and treat respiratory distress syndrome (hyaline membrane disease) in neonates and preterm neonates. Prophylactic use of a pulmonary surfactant may reduce the need for mechanical ventilation and is more effective than 'rescue treatment' in preterm neonates of 29 weeks or less corrected gestational age.

Pulmonary surfactants may also be of benefit in neonates with meconium aspiration syndrome or intrapartum streptococcal infection.

Pulmonary immaturity with surfactant deficit is the commonest reason for respiratory failure in the neonate, especially in those of less than 30 weeks corrected gestational age. Betamethasone (section 6.3.2) given to the mother (at least 12 hours but preferably 48 hours) before delivery substantially enhances pulmonary maturity in the neonate.

Side-effects Pulmonary surfactants have been associated with intracranial haemorrhage. Bradycardia, pulmonary haemorrhage, and decreased oxygen saturation have been reported rarely; hyperoxia and obstruction of the endotracheal tube by mucous secretions have also been reported.

BERACTANT

Cautions consult product literature

Side-effects see notes above

Indications and dose

Treatment of respiratory distress syndrome in preterm neonates, birth-weight over 700 g (specialist use only)

- **By endotracheal tube**

Preterm neonate phospholipid 100 mg/kg equivalent to a volume of 4 mL/kg, preferably within 8 hours of birth; dose may be repeated within 48 hours at intervals of at least 6 hours for up to 4 doses

Prophylaxis of respiratory distress syndrome in preterm neonates less than 32 weeks corrected gestational age (specialist use only)

- **By endotracheal tube**

Preterm neonate phospholipid 100 mg/kg equivalent to a volume of 4 mL/kg, preferably within 15 minutes of birth; dose may be repeated within 48 hours at intervals of at least 6 hours for up to 4 doses

Survanta® (AbbVie) (PoM)

Suspension, beractant (bovine lung extract) providing phospholipid 25 mg/mL, with lipids and proteins, net price 8-mL vial = £306.43

PORACTANT ALFA

Cautions consult product literature

Side-effects see notes above; also rarely hypotension

Indications and dose

Treatment of respiratory distress syndrome in neonates, birth-weight over 700 g (specialist use only)

- **By endotracheal tube**

Neonate 100–200 mg/kg; further doses of 100 mg/kg may be repeated at intervals of 12 hours; max. total dose 300–400 mg/kg

Prophylaxis of respiratory distress syndrome in neonates 24–31 weeks corrected gestational age (specialist use only)

- **By endotracheal tube**

Preterm neonate 100–200 mg/kg soon after birth, preferably within 15 minutes; further doses of 100 mg/kg may be repeated 6–12 hours later and after a further 12 hours if still intubated; max. total dose 300–400 mg/kg

Curosurf® (Chiesi) (PoM)

Suspension, poractant alfa (porcine lung phospholipid fraction) 80 mg/mL, net price 1.5-mL vial = £281.64; 3-mL vial = £547.40

3.6 Oxygen

Oxygen should be regarded as a drug. It is prescribed for hypoxaemic patients to increase alveolar oxygen tension and decrease the work of breathing. The concentration of oxygen required depends on the condition being treated; administration of an inappropriate concentration of oxygen may have serious or even fatal consequences. High concentrations of oxygen can cause pulmonary epithelial damage (bronchopulmonary dysplasia), convulsions, and retinal damage, especially in preterm neonates.

Oxygen is probably the most common drug used in medical emergencies. It should be prescribed initially to achieve a normal or near-normal oxygen saturation. In most acutely ill children with an expected or known normal or low arterial carbon dioxide (P_aCO_2), oxygen saturation should be maintained above 92%; some clinicians may aim for a target of 94–98%. In some clinical situations, such as carbon monoxide poisoning, (see also Emergency Treatment of Poisoning, p. 31), it is more appropriate to aim for the highest possible oxygen saturation until the child is stable. Hypercapnic respiratory failure is rare in children; in those children at risk, a lower oxygen saturation target of 88–92% is indicated, see below.

High concentration oxygen therapy is safe in uncomplicated cases of conditions such as pneumonia, pulmonary embolism, pulmonary fibrosis, shock, severe trauma, sepsis, or anaphylaxis. In such conditions, low arterial oxygen (P_aO_2) is usually associated with low or normal arterial carbon dioxide (P_aCO_2) and there is little risk of hypoventilation and carbon dioxide retention.

In severe acute asthma, the arterial carbon dioxide ($P_a\text{CO}_2$) is usually subnormal, but as asthma deteriorates it may rise steeply. These patients usually require a high concentration of oxygen and if the arterial carbon dioxide ($P_a\text{CO}_2$) remains high despite treatment, intermittent positive pressure ventilation needs to be considered urgently.

Oxygen should not be given to neonates except under expert supervision. Particular care is required in preterm neonates because of the risk of hyperoxia (see above).

Low concentration oxygen therapy (controlled oxygen therapy) is reserved for children at risk of hypercapnic respiratory failure, which is more likely in children with:

- advanced cystic fibrosis;
- advanced non-cystic fibrosis bronchiectasis;
- severe kyphoscoliosis or severe ankylosing spondylitis;
- severe lung scarring caused by tuberculosis;
- musculoskeletal disorders with respiratory weakness, especially if on home ventilation;
- an overdose of opioids, benzodiazepines, or other drugs causing respiratory depression.

Until blood gases can be measured, initial oxygen should be given using a controlled concentration of 28% or less, titrated towards a target concentration of 88–92%. The aim is to provide the child with enough oxygen to achieve an acceptable arterial oxygen tension without worsening carbon dioxide retention and respiratory acidosis.

Domiciliary oxygen Oxygen should only be prescribed for use in the home after careful evaluation in hospital by a respiratory care specialist. Carers and children who smoke should be advised of the risks of smoking when receiving oxygen, including the risk of fire. Smoking cessation therapy (section 4.10.2) should be recommended before home oxygen prescription.

Long-term oxygen therapy

The aim of long-term oxygen therapy is to maintain oxygen saturation of at least 92%. Children (especially those with chronic neonatal lung disease) often require supplemental oxygen, either for 24-hours a day or during periods of sleep; many children are eventually weaned off long-term oxygen therapy as their condition improves.

Long-term oxygen therapy should be considered for children with conditions such as:

- bronchopulmonary dysplasia (chronic neonatal lung disease);
- congenital heart disease with pulmonary hypertension;
- pulmonary hypertension secondary to pulmonary disease;
- idiopathic pulmonary hypertension;
- sickle-cell disease with persistent nocturnal hypoxia;
- interstitial lung disease and obliterative bronchiolitis;
- cystic fibrosis;
- obstructive sleep apnoea syndrome;

- neuromuscular or skeletal disease requiring non-invasive ventilation;
- pulmonary malignancy or other terminal disease with disabling dyspnoea.

Increased respiratory depression is seldom a problem in children with stable respiratory failure treated with low concentrations of oxygen although it may occur during exacerbations; children and their carers should be warned to call for medical help if drowsiness or confusion occurs.

Short-burst oxygen therapy

Oxygen is occasionally prescribed for short-burst (intermittent) use for episodes of breathlessness.

Ambulatory oxygen therapy

Ambulatory oxygen is prescribed for children on long-term oxygen therapy who need to be away from home on a regular basis.

Oxygen therapy equipment

Under the NHS oxygen may be supplied as **oxygen cylinders**. Oxygen flow can be adjusted by means of an oxygen flow meter. Oxygen delivered from a cylinder should be passed through a humidifier if used for long periods.

Oxygen concentrators are more economical for children who require oxygen for long periods, and in England and Wales can be ordered on the NHS on a regional tendering basis (see below). A concentrator is recommended for a child who requires oxygen for more than 8 hours a day (or 21 cylinders per month). Exceptionally, if a higher concentration of oxygen is required the output of 2 oxygen concentrators can be combined using a 'Y' connection.

A nasal cannula is usually preferred to a face mask for long-term oxygen therapy from an oxygen concentrator. Nasal cannulas can, however, cause dermatitis and mucosal drying in sensitive individuals.

Giving oxygen by nasal cannula allows the child to talk, eat, and drink, but the concentration is not controlled and the method may not be appropriate for acute respiratory failure. When oxygen is given through a nasal cannula at a rate of 1–2 litres/minute the inspiratory oxygen concentration is usually low, but it varies with ventilation and can be high if the child is underventilating.

Arrangements for supplying oxygen

The following services may be ordered in England and Wales:

- emergency oxygen;
- short-burst (intermittent) oxygen therapy;
- long-term oxygen therapy;
- ambulatory oxygen.

The type of oxygen service (or combination of services) should be ordered on a Home Oxygen Order Form (HOOF); the amount of oxygen required (hours per day) and flow rate should be specified. The clinician will determine the appropriate equipment to be provided. Special needs or preferences should be specified on the HOOF.

The clinician should obtain the consent of the child or carer to pass on the child's details to the supplier, the fire brigade, and other relevant organisations. The supplier will contact the child or carer to make arrangements for delivery, installation, and maintenance of the equipment. The supplier will also train the child or carer to use the equipment.

The clinician should send the HOOF to the supplier who will continue to provide the service until a revised HOOF is received, or until notified that the child no longer requires the home oxygen service.

HOOF and further instructions are available at www.bprs.co.uk/oxygen.html.

East of England
North East

BOC Medical
to order:
Tel: 0800 136 603
Fax: 0800 169 9989

South West

Air Liquide
to order:
Tel: 0808 202 2229
Fax: 0191 497 4340

London
East Midlands
North West

Air Liquide
to order:
Tel: 0500 823 773
Fax: 0800 781 4610

Yorkshire and Humberside
West Midlands
Wales

Air Products
to order:
Tel: 0800 373 580
Fax: 0800 214 709

South East Coast
South Central

Dolby Vivisol
to order:
Tel: 08443 814 402
Fax: 0800 781 4610

In **Scotland**, refer the child for assessment by a paediatric respiratory consultant. If the need for a concentrator is confirmed the consultant will arrange for the provision of a concentrator through the Common Services Agency. In **Northern Ireland** oxygen concentrators and cylinders should be prescribed on form HS21; oxygen concentrators are supplied by a local contractor. In **Scotland** and **Northern Ireland**, prescriptions for oxygen cylinders and accessories can be dispensed by pharmacies contracted to provide domiciliary oxygen services.

3.7 Mucolytics

Mucolytics, such as **carbocysteine** are used to facilitate mucociliary clearance and expectoration by reducing sputum viscosity but evidence of efficacy is limited.

Dornase alfa is a genetically engineered version of a naturally occurring human enzyme which cleaves extracellular deoxyribonucleic acid (DNA); it is used to reduce sputum viscosity in children with cystic fibrosis. Dornase alfa is administered by inhalation using a jet nebuliser (section 3.1.5), usually once daily at least 1 hour before physiotherapy; however, alternate-day therapy may be as effective as daily treatment. Not all children benefit from treatment with dornase alfa; improvement occurs within 2 weeks, but in more severely affected children a trial of 6–12 weeks may be required.

Nebulised **hypertonic sodium chloride** solution may improve mucociliary clearance in children with cystic fibrosis or bronchiolitis (see Hypertonic Sodium Chloride below).

Mesna (*Mistabron*®, available from 'special-order' manufacturers or specialist importing companies, see p. 840) is used in some children with cystic fibrosis when other mucolytics have failed to reduce sputum viscosity; 3–6 mL of a 20% solution is nebulised twice daily.

Acetylcysteine has been used to treat meconium ileus in neonates and distal intestinal obstruction syndrome in children with cystic fibrosis, but evidence of efficacy is lacking. *Gastrografin*® (section 1.6.5), or a bowel cleansing preparation containing macrogols (section 1.6.5), is usually more effective. Acetylcysteine may be used as a mucolytic to prevent further obstruction.

ACETYL CYSTEINE

Cautions history of peptic ulceration; asthma

Side-effects hypersensitivity-like reactions including rashes and anaphylaxis

Licensed use not licensed for use in meconium ileus or for distal intestinal obstructive syndrome in children with cystic fibrosis

Indications and dose

Meconium ileus (but see notes above)

- By mouth

Neonate 200–400 mg up to 3 times daily if necessary

Treatment of distal intestinal obstructive syndrome (but see notes above)

- By mouth

Child 1 month–2 years 0.4–3 g as a single dose

Child 2–7 years 2–3 g as a single dose

Child 7–18 years 4–6 g as a single dose

Prevention of distal intestinal obstruction syndrome

- By mouth

Child 1 month–2 years 100–200 mg 3 times daily

Child 2–12 years 200 mg 3 times daily

Child 12–18 years 200–400 mg 3 times daily

Administration For oral administration, use oral granules, or dilute injection solution (200 mg/mL) to a concentration of 50 mg/mL; orange or blackcurrant juice or cola drink may be used as a diluent to mask the bitter taste

Acetylcysteine (Non-proprietary) (PoM)

Oral granules, acetylcysteine 100 mg/sachet; 200 mg/sachet. Label: 13

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Injection

See Emergency treatment of poisoning, p. 27

CARBOCISTEINE

Cautions history of peptic ulceration

Contra-indications active peptic ulceration

Pregnancy manufacturer advises avoid in first trimester

Breast-feeding no information available

Side-effects rarely gastro-intestinal bleeding; also reported Stevens-Johnson syndrome, erythema multiforme

Indications and dose**Reduction of sputum viscosity**

● By mouth

Child 2–5 years 62.5–125 mg 4 times daily**Child 5–12 years** 250 mg 3 times daily**Child 12–18 years** initially 2.25 g daily in divided doses, then 1.5 g daily in divided doses as condition improves**Carbocisteine** (Non-proprietary) (PoM)**Capsules**, carbocisteine 375 mg, net price 120-cap pack = £16.64**Brands include** *Mucodyne*®**Oral liquid**, carbocisteine 125 mg/5 mL, net price 300 mL = £5.08; 250 mg/5 mL, 300 mL = £6.99**Brands include** *Mucodyne*® Paediatric 125 mg/5 mL (cherry- and raspberry-flavoured) and *Mucodyne*® 250 mg/5 mL (cinnamon- and rum-flavoured)**DORNASE ALFA**

Phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase)

Pregnancy no evidence of teratogenicity; manufacturer advises use only if potential benefit outweighs risk**Breast-feeding** amount probably too small to be harmful—manufacturer advises caution**Side-effects** pharyngitis, voice changes, chest pain; occasionally laryngitis, rashes, urticaria, conjunctivitis**Indications and dose****Management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function**

● By inhalation of nebulised solution (by jet nebuliser)

Child 5–18 years 2500 units (2.5 mg) once daily**Pulmozyme**® (Roche) (PoM)**Nebuliser solution**, dornase alfa 1000 units (1 mg)/mL. Net price 2.5-mL (2500 units) vial = £16.55**Note** For use undiluted with jet nebulisers only; ultrasonic nebulisers are unsuitable**Hypertonic sodium chloride**

Nebulised hypertonic sodium chloride solution (3–7 %) is used to mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis). Nebulised hypertonic sodium chloride solution (3%) is used for mild to moderate acute viral bronchiolitis in infants.

Temporary irritation, such as coughing, hoarseness, or reversible bronchoconstriction may occur; an inhaled bronchodilator can be used before treatment with hypertonic sodium chloride to reduce the risk of these adverse effects.

MucoClear® 3% (Pari)**Nebuliser solution**, sodium chloride 3%, net price 20 × 4 mL = £12.98; 60 × 4 mL = £27.00**Dose**

● By inhalation of nebulised solution

Child 4 mL 2–4 times daily**MucoClear**® 6% (Pari)**Nebuliser solution**, sodium chloride 6%, net price 20 × 4 mL = £12.98; 60 × 4 mL = £27.00**Dose**

● By inhalation of nebulised solution

Child 4 mL twice daily**Nebusa**® 7% (Forest)**Nebuliser solution**, sodium chloride 7%, net price 60 × 4 mL = £27.00**Dose**

● By inhalation of nebulised solution

Child 4 mL up to twice daily**Ivacaftor**

Ivacaftor is licensed for the treatment of cystic fibrosis in children who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; it should be prescribed by a physician experienced in the treatment of cystic fibrosis. If the child's genotype is unknown, a validated genotyping method should be performed to confirm the presence of the G551D mutation in at least one allele of the CFTR gene before starting treatment.

IVACAFTOR**Cautions** test liver function before treatment, every 3 months during the first year of treatment, then annually thereafter; **interactions:** Appendix 1 (ivacaftor)**Contra-indications** organ transplantation (no information available); avoid grapefruit and Seville oranges**Hepatic impairment** max. 150 mg once daily in moderate impairment; in severe impairment, manufacturer recommends use only if potential benefit outweighs risk—starting dose 150 mg on alternate days, dosing interval adjusted according to clinical response and tolerability**Renal impairment** caution in severe impairment**Pregnancy** manufacturer advises use only if potential benefit outweighs risk—no information available**Breast-feeding** manufacturer advises use only if potential benefit outweighs risk—no information available**Side-effects** abdominal pain, diarrhoea, oropharyngeal pain, pharyngeal oedema, headache, dizziness, upper respiratory-tract infection, rhinitis, nasopharyngitis, nasal congestion, ear discomfort, tinnitus, rash; *less commonly* vestibular disorder, gynaecomastia**Indications and dose****Treatment of cystic fibrosis in children who have a G551D mutation in the CFTR gene**

● By mouth

Child 6–18 years 150 mg every 12 hours**Note** Reduce dose to 150 mg twice a week with concomitant use of itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin; reduce dose to 150 mg once daily with concomitant use of fluconazole and erythromycin**Kalydeco**® (Vertex) ▼ (PoM)**Tablets**, f/c, ivacaftor 150 mg, net price 56-tab pack = £14000.00. Label: 25, counselling, administration**Counselling** Tablets should be taken with fat-containing food

3.8 Aromatic inhalations

Inhalations containing volatile substances such as eucalyptus oil are traditionally used to relieve congestion and ease breathing. Although the vapour may contain little of the additive, it encourages deliberate inspiration of warm moist air which is often comforting. Boiling water should not be used for inhalations owing to the risk of scalding.

Strong aromatic decongestants (applied as rubs or to pillows) are not recommended for infants under the age of 3 months. **Sodium chloride 0.9%** solution given as nasal drops can be used to liquefy mucous secretions and relieve nasal congestion in infants and young children; administration before feeds may ease feeding difficulties caused by nasal congestion.

Benzoïn Tincture, Compound, BP (Friars' Balsam)

Tincture, balsamic acids approx. 4.5%. Label: 15

Side-effects allergic contact dermatitis

Dose

Nasal congestion

• By inhalation

Add 5 mL to a pint of hot, **not** boiling, water and inhale the vapour; repeat after 4 hours if necessary

Menthol and Eucalyptus Inhalation, BP 1980

Inhalation, racementhol or levomenthol 2 g, eucalyptus oil 10 mL, light magnesium carbonate 7 g, water to 100 mL

Dose

Nasal congestion

• By inhalation

Add one teaspoonful to a pint of hot, **not** boiling, water and inhale the vapour

Dental prescribing on the NHS May be prescribed as Menthol and Eucalyptus Inhalation BP, 1980

3.9 Cough preparations

3.9.1 Cough suppressants

3.9.2 Expectorant and demulcent cough preparations

3.9.1 Cough suppressants

Cough may be a symptom of an underlying disorder such as asthma (section 3.1), gastro-oesophageal reflux disease (section 1.1), or rhinitis (section 12.2.1), which should be addressed before prescribing cough suppressants. Cough may be associated with smoking or environmental pollutants. Cough can also result from bronchiectasis including that associated with cystic fibrosis; cough can also have a significant habit component. There is little evidence of any significant benefit from the use of cough suppressants in children with acute cough in ambulatory settings. Cough suppressants may cause sputum retention and this can be harmful in children with bronchiectasis.

The use of cough suppressants containing **pholcodine** or similar opioid analgesics is not generally recommended in children and should be avoided in children under 6 years; the use of over-the-counter codeine-containing liquids should be avoided in children under 18 years, see MHRA/CHM advice below.

Sedating antihistamines (section 3.4.1) are used as the cough suppressant component of many compound cough preparations on sale to the public; all tend to cause drowsiness which may reflect their main mode of action.

MHRA/CHM advice (March 2008 and February 2009)

Children under 6 years should not be given over-the-counter cough and cold medicines containing the following ingredients:

- brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine, or triprolidine (antihistamines);
- dextromethorphan or pholcodine (cough suppressants);
- guaifenesin or ipecacuanha (expectorants);
- phenylephrine, pseudoephedrine, ephedrine, oxymetazoline, or xylometazoline (decongestants).

Over-the-counter cough and cold medicines can be considered for children aged 6–12 years after basic principles of best care have been tried, but treatment should be restricted to five days or less. Children should not be given more than 1 cough or cold preparation at a time because different brands may contain the same active ingredient; care should be taken to give the correct dose.

MHRA/CHM advice (October 2010) Over-the-counter codeine-containing liquid medicines for children

Children under 18 years should not use codeine-containing over-the-counter liquid medicines for cough suppression

PHOLCODINE

Cautions asthma; chronic, persistent, or productive cough; **interactions:** Appendix 1 (pholcodine)

Contra-indications chronic bronchitis, bronchiectasis, bronchiolitis, children at risk of respiratory failure

Hepatic impairment avoid

Renal impairment use with caution; avoid in severe impairment

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk

Breast-feeding manufacturer advises avoid unless potential benefit outweighs risk—no information available

Side-effects nausea, vomiting, constipation, sputum retention, drowsiness, dizziness, excitation, confusion, rash

Indications and dose

Dry cough (but not generally recommended for children, see notes above)

• By mouth

Child 6–12 years 2–5 mg 3–4 times daily

Child 12–18 years 5–10 mg 3–4 times daily

Pholcodine Linctus, BP

Linctus (= oral solution), pholcodine 5 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 1%. Net price 100 mL = 31p

Brands include Pavacol-D® (sugar-free), Galenphol® (sugar-free)

Pholcodine Linctus, Strong, BP

Linctus (= oral solution), pholcodine 10 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 2%. Net price 100 mL = 44p

Brands include *Galenphol*[®]

Galenphol[®] (Thornton & Ross)

Paediatric linctus (= oral solution), orange, sugar-free, pholcodine 2 mg/5 mL. Net price 100 mL = £0.19

3.9.2 Expectorant and demulcent cough preparations

Simple linctus and other demulcent cough preparations containing soothing substances, such as syrup or glycerol, may temporarily relieve a dry irritating cough. These preparations have the advantage of being harmless and inexpensive and sugar-free versions are available.

Expectorants are claimed to promote expulsion of bronchial secretions but there is no evidence that any drug can specifically facilitate expectoration.

Compound cough preparations for children are on sale to the public but should not be used in children under 6 years; the rationale for some is dubious. Care should be taken to give the correct dose and to not use more than one preparation at a time, see MHRA/CHM advice p. 166.

Simple Linctus, Paediatric, BP

Linctus (= oral solution), citric acid monohydrate 0.625% in a suitable vehicle with an anise flavour, net price 200 mL = 96p

A sugar-free version is also available

Dose**Cough**

- By mouth

Child 1 month–12 years 5–10 mL 3–4 times daily

Simple Linctus, BP

Linctus (= oral solution), citric acid monohydrate 2.5% in a suitable vehicle with an anise flavour, net price 200 mL = 92p

A sugar-free version is also available

Dose**Cough**

- By mouth

Child 12–18 years 5 mL 3–4 times daily

3.10 Systemic nasal decongestants

Nasal congestion in children due to allergic or vasomotor rhinitis should be treated with oral antihistamines (section 3.4.1), topical nasal preparations containing corticosteroids (section 12.2.1), or topical decongestants (section 12.2.2).

There is little evidence to support the use of systemic decongestants in children.

Pseudoephedrine has few sympathomimetic effects, and is commonly combined with other ingredients (including antihistamines) in preparations intended for the relief of cough and cold symptoms but it should not be used in children under 6 years, see MHRA/CHM advice, p. 166.

PSEUDOEPHEDRINE HYDROCHLORIDE

Cautions hypertension, heart disease, diabetes, hyperthyroidism, raised intra-ocular pressure; **interactions:** Appendix 1 (sympathomimetics)

Contra-indications treatment with MAOI within previous 2 weeks

Hepatic impairment manufacturer advises caution in severe impairment

Renal impairment caution in mild to moderate impairment; manufacturer advises avoid in severe impairment

Pregnancy defective closure of the abdominal wall (gastrochisis) reported very rarely in newborns after first trimester exposure

Breast-feeding may suppress lactation; avoid if lactation not well established or if milk production insufficient

Side-effects nausea, vomiting, hypertension, tachycardia, headache, anxiety, restlessness, insomnia; rarely hallucinations, rash; urinary retention also reported

Indications and dose

Congestion of mucous membranes of upper respiratory tract

- By mouth

Child 6–12 years 30 mg 3–4 times daily

Child 12–18 years 60 mg 3–4 times daily

¹Galpseud[®] (Thornton & Ross) (PoM) 

Tablets, pseudoephedrine hydrochloride 60 mg, net price 24 = £2.25

Linctus, orange, sugar-free, pseudoephedrine hydrochloride 30 mg/5 mL, net price 100 mL = £0.70

Excipients include alcohol

¹Sudafed[®] (McNeil) (PoM) 

Tablets, red, f/c, pseudoephedrine hydrochloride 60 mg, net price 24 = £2.12

Elixir, red, pseudoephedrine hydrochloride 30 mg/5 mL, net price 100 mL = £1.10

3.11 Antifibrotics

Classification not used in *BNF for Children*

1. Can be sold to the public provided no more than 720 mg of pseudoephedrine salts are supplied, and ephedrine base (or salts) are not supplied at the same time; for details see *Medicines, Ethics and Practice*, London, Pharmaceutical Press (always consult latest edition)

4 Central nervous system

4.1 Hypnotics and anxiolytics	168
4.1.1 Hypnotics	168
4.1.2 Anxiolytics	170
4.1.3 Barbiturates	170
4.2 Drugs used in psychoses and related disorders	170
4.2.1 Antipsychotic drugs	171
4.2.2 Antipsychotic depot injections	181
4.2.3 Drugs used for mania and hypomania	181
4.3 Antidepressant drugs	183
4.3.1 Tricyclic antidepressant drugs	184
4.3.2 Monoamine-oxidase inhibitors	186
4.3.3 Selective serotonin re-uptake inhibitors	186
4.3.4 Other antidepressant drugs	188
4.4 CNS stimulants and other drugs for attention deficit hyperactivity disorder	188
4.5 Drugs used in the treatment of obesity	191
4.6 Drugs used in nausea and vertigo	192
4.7 Analgesics	199
4.7.1 Non-opioid analgesics and compound analgesic preparations	199
4.7.2 Opioid analgesics	203
4.7.3 Neuropathic pain	213
4.7.4 Antimigraine drugs	213
4.7.4.1 Treatment of acute migraine	213
4.7.4.2 Prophylaxis of migraine	215
4.7.4.3 Cluster headache and the trigeminal autonomic cephalalgias	215
4.8 Antiepileptics	216
4.8.1 Control of the epilepsies	216
4.8.2 Drugs used in status epilepticus	236
4.8.3 Febrile convulsions	239
4.9 Drugs used in dystonias and related disorders	239
4.9.1 Dopaminergic drugs used in dystonias	239
4.9.2 Antimuscarinic drugs used in dystonias	241

4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders	241
4.10 Drugs used in substance dependence	242
4.10.1 Alcohol dependence	242
4.10.2 Nicotine dependence	242
4.10.3 Opioid dependence	245
4.11 Drugs for dementia	245

4.1 Hypnotics and anxiolytics

4.1.1 Hypnotics
4.1.2 Anxiolytics
4.1.3 Barbiturates

Most anxiolytics ('sedatives') will induce sleep when given at night and most hypnotics will sedate when given during the day. Hypnotics and anxiolytics should be reserved for short courses to alleviate acute conditions after causal factors have been established.

The role of drug therapy in the management of anxiety disorders in children and adolescents is uncertain; drug therapy should be initiated only by specialists after psychosocial interventions have failed. Benzodiazepines and tricyclic antidepressants have been used but adverse effects may be problematic.

Skilled tasks Hypnotics and anxiolytics may impair judgement and increase reaction time, and so affect ability to drive or perform skilled tasks; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair performance on the following day.

Important

1. Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling or causing the child unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness.
2. The use of benzodiazepines to treat short-term 'mild' anxiety is inappropriate.
3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or causing the child extreme distress.

4.1.1 Hypnotics

The prescribing of hypnotics to children, except for occasional use such as for sedation for procedures (section 15.1.4), is not justified. There is a risk of habituation with prolonged use. Problems settling chil-

dren at night should be managed with behavioural therapy.

Dental procedures Some anxious children may benefit from the use of a hypnotic the night before the dental appointment.

Chloral and derivatives

Chloral hydrate and derivatives were formerly popular hypnotics for children.

Chloral hydrate is now mainly used for sedation during diagnostic procedures (section 15.1.4). It accumulates on prolonged use.

CHLORAL HYDRATE

Cautions reduce dose in debilitated; avoid prolonged use (and abrupt withdrawal thereafter); avoid contact with skin and mucous membranes; **interactions:** Appendix 1 (anxiolytics and hypnotics)

Skilled tasks Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications severe cardiac disease; gastritis; acute porphyria (section 9.8.2)

Hepatic impairment can precipitate coma; reduce dose in mild to moderate hepatic impairment; avoid in severe impairment

Renal impairment avoid in severe impairment

Pregnancy avoid

Breast-feeding risk of sedation in infant—avoid

Side-effects gastric irritation (nausea and vomiting reported), abdominal distention, flatulence, headache, tolerance, dependence, excitement, delirium (especially on abrupt withdrawal), ketonuria, and rash

Licensed use not licensed for sedation for painless procedures

Indications and dose

Sedation for painless procedures

- By mouth or by rectum (if oral route not available)

Neonate 30–50 mg/kg 45–60 minutes before procedure; doses up to 100 mg/kg may be used with respiratory monitoring

Child 1 month–12 years 30–50 mg/kg (max. 1 g) 45–60 minutes before procedure; higher doses up to 100 mg/kg (max. 2 g) may be used

Child 12–18 years 1–2 g 45–60 minutes before procedure

Administration for administration *by mouth* dilute liquid with plenty of water or juice to mask unpleasant taste.

Chloral Mixture, BP 2000 [PoM]

(Chloral Oral Solution)

Mixture, chloral hydrate 500 mg/5 mL in a suitable vehicle. Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Chloral Elixir, Paediatric, BP 2000 [PoM]

(Chloral Oral Solution, Paediatric)

Elixir, chloral hydrate 200 mg/5 mL (4%) in a suitable vehicle with a black currant flavour. Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Chloral Hydrate (Non-proprietary) [PoM]

Suppositories, chloral hydrate 25 mg, 50 mg, 60 mg, 100 mg, 200 mg, 500 mg. Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Chloral betaine

Welldorm® (Marlborough) [PoM]

Tablets, blue-purple, f/c, chloral betaine 707 mg (= chloral hydrate 414 mg), net price 30-tab pack = £12.10. Label: 19, 27

Dose

Short-term treatment of insomnia

- By mouth

Child 12–18 years 1–2 tablets with water or milk at bedtime, max. 5 tablets (chloral hydrate 2 g) daily

Elixir, red, chloral hydrate 143.3 mg/5 mL, net price 150-mL pack = £8.70. Label: 19, 27

Dose

Short-term treatment of insomnia

- By mouth

Child 2–12 years 1–1.75 mL/kg (chloral hydrate 30–50 mg/kg) with water or milk at bedtime; max. 35 mL (chloral hydrate 1 g) daily

Child 12–18 years 15–45 mL (chloral hydrate 0.4–1.3 g) with water or milk at bedtime; max. 70 mL (chloral hydrate 2 g) daily

Antihistamines

Some **antihistamines** (section 3.4.1) such as promethazine are used for occasional insomnia in adults; their prolonged duration of action can often cause drowsiness the following day. The sedative effect of antihistamines may diminish after a few days of continued treatment; antihistamines are associated with headache, psychomotor impairment and antimuscarinic effects.

The use of antihistamines as hypnotics in children is not usually justified.

PROMETHAZINE HYDROCHLORIDE

Cautions see notes in section 3.4.1; also avoid extravasation with intravenous injection

Contra-indications see Promethazine Hydrochloride, section 3.4.1

Hepatic impairment see notes in section 3.4.1

Renal impairment see Promethazine Hydrochloride, section 3.4.1

Pregnancy see notes in section 3.4.1

Breast-feeding see notes in section 3.4.1

Side-effects see Promethazine Hydrochloride, section 3.4.1

Licensed use not licensed for use in children under 2 years

Indications and dose

Sedation (short-term use)

- By mouth

Child 2–5 years 15–20 mg

Child 5–10 years 20–25 mg

Child 10–18 years 25–50 mg

Sedation in intensive care

- By mouth or by slow intravenous injection or by deep intramuscular injection

Child 1 month–12 years 0.5–1 mg/kg (max. 25 mg) 4 times daily, adjusted according to response

Child 12–18 years 25–50 mg 4 times daily, adjusted according to response

Allergy and urticaria section 3.4.1**Nausea and vomiting** section 4.6**¹Promethazine** (Non-proprietary) (PoM)

Injection, promethazine hydrochloride 25 mg/mL, net price 1-mL amp = 68p, 2-mL amp = £1.20

¹Phenergan® (Sanofi-Aventis) (PoM)

Injection, promethazine hydrochloride 25 mg/mL, net price 1-mL amp = 67p
Excipients include sulfites

Oral preparations

Section 3.4.1

Melatonin

Melatonin is a pineal hormone that may affect sleep pattern. Clinical experience suggests that when appropriate behavioural sleep interventions fail, melatonin may be of value for treating sleep onset insomnia and delayed sleep phase syndrome in children with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder, autism, and learning difficulties. It is also sometimes used before magnetic resonance imaging (MRI), computed tomography (CT), or EEG investigations. Little is known about its long-term effects in children, and there is uncertainty as to the effect on other circadian rhythms including endocrine or reproductive hormone secretion. Treatment with melatonin should be initiated and supervised by a specialist, but may be continued by general practitioners under a shared-care arrangement. The need to continue melatonin therapy should be reviewed every 6 months.

Melatonin is available as a modified-release tablet (*Circadin*®) and also as unlicensed formulations. *Circadin*® is licensed for the short-term treatment of primary insomnia in adults over 55 years. Unlicensed immediate-release preparations are available; the manufacturer should be specified in the shared-care guideline because of variability in clinical effect of unlicensed formulations.

MELATONIN

Cautions autoimmune disease (manufacturer advises avoid—no information available); **interactions:** Appendix 1 (melatonin)

Hepatic impairment clearance reduced—manufacturer advises avoid

Renal impairment no information available—caution

Pregnancy no information available—avoid

Breast-feeding present in milk—avoid

Side-effects less commonly abdominal pain, dyspepsia, dry mouth, mouth ulceration, nausea, weight

¹ (PoM) restriction does not apply where administration is for saving life in emergency

gain, hypertension, chest pain, malaise, dizziness, restlessness, nervousness, irritability, anxiety, headache, abnormal dreams, proteinuria, glycosuria, pruritus, rash, dry skin; rarely thirst, flatulence, halitosis, hypersalivation, vomiting, gastritis, hypertriglyceridaemia, palpitation, syncope, hot flushes, aggression, impaired memory, restless legs syndrome, paraesthesia, mood changes, priapism, increased libido, prostatitis, polyuria, haematuria, leucopenia, thrombocytopenia, electrolyte disturbances, muscle spasm, arthritis, lacrimation, visual disturbances, nail disorder; also reported galactorrhoea, mouth and tongue oedema

Licensed use not licensed for use in children

Indications and dose

Sleep onset insomnia and delayed sleep phase syndrome (see notes above)

- By mouth

Child 1 month–18 years initially 2–3 mg daily before bedtime increased if necessary after 1–2 weeks to 4–6 mg daily before bedtime; max. 10 mg daily

Circadin® (Flynn) (PoM)

Tablets, m/r, melatonin 2 mg, net price 30-tab pack = £15.39. Label: 2, 21, 25

Note Other formulations of melatonin are available from 'special-order' manufacturers or specialist importing companies, see p. 840

4.1.2 Anxiolytics

Anxiolytic treatment should be used in children only to relieve acute anxiety (and related insomnia) caused by fear (e.g. before surgery, section 15.1.4.1).

Anxiolytic treatment should be limited to the lowest possible dose for the shortest possible time (see p. 168).

Buspirone

Buspirone is thought to act at specific serotonin (5HT_{1A}) receptors; safety and efficacy in children have yet to be determined.

4.1.3 Barbiturates

Classification not used in *BNF for Children*.

4.2 Drugs used in psychoses and related disorders**4.2.1 Antipsychotic drugs****4.2.2 Antipsychotic depot injections****4.2.3 Drugs used for mania and hypomania**

Advice on doses of antipsychotic drugs above *BNF for Children* upper limit

1. Consider alternative approaches including adjuvant therapy.
2. Bear in mind risk factors, including obesity.
3. Consider potential for drug interactions—see **interactions:** Appendix 1 (antipsychotics).
4. Carry out ECG to exclude untoward abnormalities such as prolonged QT interval; repeat ECG periodically.

cally and reduce dose if prolonged QT interval or other adverse abnormality develops.

5. Increase dose slowly and not more often than once weekly.
6. Carry out regular pulse, blood pressure, and temperature checks; ensure that patient maintains adequate fluid intake.
7. Consider high-dose therapy to be for limited period and review regularly; abandon if no improvement after 3 months (return to standard dosage).

Important When prescribing an antipsychotic for administration on an emergency basis, the intramuscular dose should be **lower** than the corresponding oral dose (owing to absence of first-pass effect), particularly if the child is very active (increased blood flow to muscle considerably increases the rate of absorption). The prescription should specify the dose for **each route** and should not imply that the same dose can be given by mouth or by intramuscular injection. The dose of antipsychotic for emergency use should be reviewed at least **daily**.

4.2.1 Antipsychotic drugs

There is little information on the efficacy and safety of antipsychotic drugs in children and adolescents and much of the information available has been extrapolated from adult data; in particular, little is known about the long-term effects of antipsychotic drugs on the developing nervous system. Antipsychotic drugs should be initiated and managed under the close supervision of an appropriate specialist.

Antipsychotic drugs are also known as 'neuroleptics' and (misleadingly) as 'major tranquillisers'.

In the short term they are used to calm disturbed children whatever the underlying psychopathology, which may be schizophrenia, brain damage, mania, toxic delirium, or agitated depression. Antipsychotic drugs are used to alleviate severe anxiety but this too should be a short-term measure.

Schizophrenia The aim of the treatment is to alleviate the suffering of the child (and carer) and to improve social and cognitive functioning. Many children require life-long treatment with antipsychotic medication. Antipsychotic drugs relieve positive psychotic symptoms such as thought disorder, hallucinations, and delusions, and prevent relapse; they are usually less effective on negative symptoms such as apathy and social withdrawal. In many patients, negative symptoms persist between episodes of treated positive symptoms, but earlier treatment of psychotic illness may protect against the development of negative symptoms over time. Children with acute schizophrenia generally respond better than those with chronic symptoms.

Long-term treatment of a child with a definitive diagnosis of schizophrenia is usually required after the first episode of illness in order to prevent relapses. Doses that are effective in acute episodes should generally be continued as prophylaxis.

First-generation antipsychotic drugs The first-generation antipsychotic drugs act predominantly by blocking dopamine D_2 receptors in the brain. First-generation antipsychotic drugs are not selective for any of the four dopamine pathways in the brain and so can cause a range of side-effects, particularly extrapyramidal symptoms and elevated prolactin. The **phenothiazine** derivatives can be divided into 3 main groups

Group 1: chlorpromazine, levomepromazine, and promazine, generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal side-effects.

Group 2: pericyazine and pipotiazine, generally characterised by moderate sedative effects, but fewer extrapyramidal side-effects than groups 1 or 3.

Group 3: perphenazine, prochlorperazine, and trifluoperazine, generally characterised by fewer sedative effects and antimuscarinic effects, but more pronounced extrapyramidal side-effects than groups 1 and 2.

Butyrophenones (e.g. haloperidol) resemble the *group 3* phenothiazines in their clinical properties. **Diphenylbutylpiperidines** (pimozide) and the **substituted benzamides** (sulpiride) have reduced sedative, antimuscarinic, and extrapyramidal effects.

Second-generation antipsychotic drugs The second-generation antipsychotic drugs (also referred as atypical antipsychotic drugs) act on a range of receptors in comparison to first-generation antipsychotic drugs and have more distinct clinical profiles, particularly with regard to side-effects.

Amisulpride is a selective dopamine receptor antagonist with high affinity for mesolimbic D_2 and D_3 receptors; **clozapine** is a dopamine D_1 , D_2 , 5-HT $_{2A}$, α_1 -adrenoceptor, and muscarinic receptor antagonist; **olanzapine** is a dopamine D_1 , D_2 , D_4 , 5-HT $_{2A}$, histamine-1, and muscarinic receptor antagonist; **quetiapine** is a dopamine D_1 , D_2 , 5-HT $_{2A}$, α_1 -adrenoceptor, and histamine-1 receptor antagonist; and **risperidone** is a dopamine D_2 , 5-HT $_{2A}$, α_1 -adrenoceptor, and histamine-1 receptor antagonist.

Aripiprazole is a dopamine D_2 partial agonist with weak 5-HT $_{1A}$ partial agonism and 5-HT $_{2A}$ receptor antagonism. Aripiprazole can cause nausea and, unlike other antipsychotic drugs, lowers prolactin.

NICE guidance

Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years (January 2011)

Aripiprazole is recommended as an option for the treatment of schizophrenia in adolescents aged 15 to 17 years who have not responded adequately to, or who are intolerant of, risperidone, or for whom risperidone is contra-indicated.

www.nice.org.uk/TA213

NICE guidance

Aripiprazole for the treatment of moderate to severe manic episodes in adolescents with bipolar I disorder (July 2013)

Aripiprazole is recommended as an option for the treatment of moderate to severe manic episodes for up to 12 weeks in adolescents aged over 13 years with bipolar I disorder.

www.nice.org.uk/TA292

Cautions Antipsychotic drugs should be used with **caution** in children with cardiovascular disease; an ECG may be required (see individual drug monographs), particularly if physical examination identifies cardiovascular risk factors, if there is a personal history of cardi-

ovascular disease, or if the child is being admitted as an inpatient. Antipsychotic drugs should also be used with caution in children with epilepsy (and conditions predisposing to seizures), pericyclic, myasthenia gravis (avoid chlorpromazine, pericyazine and prochlorperazine) or a susceptibility to angle-closure glaucoma. Caution is also required in severe respiratory disease and in children with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops). As photosensitisation may occur with higher dosages, children should avoid direct sunlight. **Interactions:** Appendix 1 (antipsychotics).

Contra-indications Antipsychotic drugs may be **contra-indicated** in comatose states, CNS depression, and phaeochromocytoma.

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced.

Withdrawal There is a high risk of relapse if medication is stopped after 1–2 years. Withdrawal of antipsychotic drugs after long-term therapy should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid relapse. Children should be monitored regularly for signs and symptoms of relapse for 2 years after withdrawal of antipsychotic medication.

Hepatic impairment All antipsychotic drugs can precipitate coma if used in hepatic impairment; phenothiazines are hepatotoxic. See also under individual drugs.

Renal impairment Start with small doses of antipsychotic drugs in severe renal impairment because of increased cerebral sensitivity. See also under individual drugs.

Pregnancy Extrapyramidal effects and withdrawal syndrome have been reported occasionally in the neonate when antipsychotic drugs are taken during the third trimester of pregnancy. Following maternal use of antipsychotic drugs in the third trimester, neonates should be monitored for symptoms including agitation, hyper-tonia, hypotonia, tremor, drowsiness, feeding problems, and respiratory distress. See also under individual drugs.

Breast-feeding There is limited information available on the short- and long-term effects of antipsychotics on the breast-fed infant. *Animal* studies indicate possible adverse effects of antipsychotic medicines on the developing nervous system. Chronic treatment with antipsychotic drugs whilst breast-feeding should be avoided unless absolutely necessary. Phenothiazine derivatives are sometimes used in breast-feeding women for short-term treatment of nausea and vomiting. See also under individual drugs.

Side-effects Side-effects caused by antipsychotic drugs are common and contribute significantly to non-adherence to therapy. Extrapyramidal symptoms occur most frequently with the group 3 phenothiazine derivatives (perphenazine, prochlorperazine, and trifluoperazine), the butyrophenones (haloperidol), and the first-generation depot preparations. They are easy to recognise but cannot be predicted accurately because they depend on the dose, the type of drug, and on individual susceptibility.

Extrapyramidal symptoms consist of:

- *parkinsonian symptoms* (including tremor), which may appear gradually (but less commonly than in adults);
- *dystonia* (abnormal face and body movements) and *dyskinesia*, which appear after only a few doses;
- *akathisia* (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated;
- *tardive dyskinesia* (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops on long-term therapy or with high dosage, but it may develop on short-term treatment with low doses—short-lived tardive dyskinesia may occur after withdrawal of the drug.

Parkinsonian symptoms remit if the drug is withdrawn and may be suppressed by the administration of **antimuscarinic** drugs (section 4.9.2). However, routine administration of such drugs is not justified because not all children are affected and because they may unmask or worsen tardive dyskinesia.

Tardive dyskinesia is the most serious manifestation of extrapyramidal symptoms; it is of particular concern because it may be irreversible on withdrawing therapy and treatment is usually ineffective. In children, tardive dyskinesia is more likely to occur when the antipsychotic drug is withdrawn. However, some manufacturers suggest that drug withdrawal at the earliest signs of tardive dyskinesia (fine vermicular movements of the tongue) may halt its full development. Tardive dyskinesia may occur and treatment must be carefully and regularly reviewed.

Most antipsychotic drugs, both first- and second-generation, increase prolactin concentration to some extent because dopamine inhibits prolactin release. Aripiprazole reduces prolactin because it is a dopamine-receptor partial agonist. Risperidone, amisulpride, and first-generation antipsychotic drugs are most likely to cause symptomatic hyperprolactinaemia. The clinical symptoms of hyperprolactinaemia include sexual dysfunction, reduced bone mineral density, menstrual disturbances, breast enlargement, and galactorrhoea.

Sexual dysfunction is one of the main causes of non-adherence to antipsychotic medication; physical illness, psychiatric illness, and substance misuse are contributing factors. Antipsychotic-induced sexual dysfunction is caused by more than one mechanism. Reduced dopamine transmission and hyperprolactinaemia decrease libido; antimuscarinic effects can cause disorders of arousal; and alpha₁-adrenoceptor antagonists are associated with erection and ejaculation problems in males. Risperidone and haloperidol commonly cause sexual dysfunction. If sexual dysfunction is thought to be antipsychotic-induced, dose reduction or switching medication should be considered.

Antipsychotic drugs have been associated with cardiovascular side-effects such as tachycardia, arrhythmias (see under Monitoring), and hypotension (see below). QT-interval prolongation is a particular concern with pimozide (see ECG monitoring in pimozide monograph) and haloperidol. There is also a higher probability of QT-interval prolongation in patients using any intravenous antipsychotic drug, or any antipsychotic drug or combination of antipsychotic drugs with doses exceeding the recommended maximum. Cases of sudden death have occurred.

Hyperglycaemia and sometimes diabetes can occur with antipsychotic drugs, particularly clozapine, olanzapine, quetiapine, and risperidone. All antipsychotic drugs may cause weight gain, but the risk and extent varies. Clozapine and olanzapine commonly cause weight gain.

Hypotension and interference with temperature regulation are dose-related side-effects. Clozapine, chlorpromazine, and quetiapine can cause postural hypotension (especially during initial dose titration) which may be associated with syncope or reflex tachycardia in some children.

Neuroleptic malignant syndrome (hyperthermia, fluctuating level of consciousness, muscle rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating, and urinary incontinence) is a rare but potentially fatal side-effect of all antipsychotic drugs. Discontinuation of the antipsychotic drug is essential because there is no proven effective treatment, but bromocriptine, and dantrolene (p. 654) have been used. The syndrome, which usually lasts for 5–7 days after drug discontinuation, may be unduly prolonged if depot preparations have been used.

Hypersalivation associated with clozapine therapy can be treated with hyoscine hydrobromide [unlicensed indication] (p. 198), provided that the patient is not at particular risk from the additive antimuscarinic side-effects of hyoscine and clozapine.

Other side-effects include: drowsiness; apathy; agitation, excitement and insomnia; convulsions; dizziness; headache; confusion; gastro-intestinal disturbances; nasal congestion; antimuscarinic symptoms (such as dry mouth, constipation, difficulty with micturition, and blurred vision; *very rarely* precipitation of angle-closure glaucoma); venous thromboembolism; blood dyscrasias (such as agranulocytosis and leucopenia), photosensitisation, contact sensitisation and rashes, and jaundice (including cholestatic); corneal and lens opacities, and purplish pigmentation of the skin, cornea, conjunctiva, and retina.

Overdosage: for poisoning with phenothiazines and related compounds and second-generation antipsychotic drugs, see Emergency Treatment of Poisoning, p. 30.

Choice The antipsychotic drugs most commonly used in children are haloperidol, risperidone, and olanzapine. There is little meaningful difference in efficacy between each of the antipsychotic drugs (other than clozapine), and response and tolerability to each antipsychotic drug varies. There is no first-line antipsychotic drug which is suitable for all children. Choice of antipsychotic medication is influenced by the child's medication history, the degree of sedation required (although tolerance to this usually develops), and consideration of individual patient factors such as risk of extrapyramidal side-effects, weight gain, impaired glucose tolerance, QT-interval prolongation, or the presence of negative symptoms.

Second-generation antipsychotic drugs may be better at treating the negative symptoms of schizophrenia. Similarly, second-generation antipsychotic drugs may be prescribed if extrapyramidal side-effects are a particular concern. Of these, aripiprazole, clozapine, olanzapine, and quetiapine are least likely to cause extrapyramidal side-effects. Although amisulpride is a dopamine-receptor antagonist, extrapyramidal side-effects are less com-

mon than with the first-generation antipsychotic drugs because amisulpride selectively blocks mesolimbic dopamine receptors, and extrapyramidal symptoms are caused by blockade of the striatal dopamine pathway.

Aripiprazole has negligible effect on the QT-interval. Other antipsychotic drugs with a reduced tendency to prolong QT-interval include amisulpride, clozapine, olanzapine, perphenazine, risperidone, and sulpiride.

Schizophrenia is associated with insulin resistance and diabetes; the risk of diabetes is increased in children with schizophrenia who take antipsychotic drugs. First-generation antipsychotic drugs are less likely to cause diabetes than second-generation antipsychotic drugs, and of the first-generation antipsychotic drugs, haloperidol has the lowest risk. Amisulpride and aripiprazole have the lowest risk of diabetes of the second-generation antipsychotic drugs. Amisulpride, aripiprazole, haloperidol, sulpiride, and trifluoperazine are least likely to cause weight gain.

The antipsychotic drugs with the lowest risk of sexual dysfunction are aripiprazole and quetiapine. Olanzapine may be considered if sexual dysfunction is judged to be secondary to hyperprolactinaemia. Hyperprolactinaemia is usually not clinically significant with aripiprazole, clozapine, olanzapine, and quetiapine treatment. When changing from other antipsychotic drugs a reduction in prolactin concentration may increase fertility.

Children should receive an antipsychotic drug for 4–6 weeks (but see clozapine below) before it is deemed ineffective. Prescribing more than one antipsychotic drug at a time should be avoided except in exceptional circumstances (e.g. clozapine augmentation or when changing medication during titration) because of the increased risk of adverse effects such as extrapyramidal symptoms, QT-interval prolongation, and sudden cardiac death.

Clozapine is used for the treatment of schizophrenia in children unresponsive to, or intolerant of, other antipsychotic drugs. Clozapine should be introduced if schizophrenia is not controlled despite the sequential use of two or more antipsychotic drugs (one of which should be a second-generation antipsychotic drug), each for at least 6–8 weeks. If symptoms do not respond adequately to an optimised dose of clozapine, plasma-clozapine concentration should be checked before adding a second antipsychotic drug to augment clozapine; allow 8–10 weeks' treatment to assess response. Children must be registered with a clozapine patient monitoring service (see under Clozapine).

Monitoring Full blood count, urea and electrolytes, and liver function test monitoring is required at the start of therapy with antipsychotic drugs, and then annually thereafter. Amisulpride and sulpiride do not require liver function test monitoring. Clozapine requires differential white blood cell monitoring weekly for 18 weeks, then fortnightly for up to one year, and then monthly as part of the clozapine patient monitoring service.

Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly. Children taking clozapine or olanzapine require more frequent monitoring of these parameters: every 3 months for the first year, then yearly.

Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly. Children taking clo-

apine or olanzapine should have fasting blood glucose tested at baseline, after one month's treatment, then every 4–6 months.

Before initiating antipsychotic drugs, an ECG may be required, particularly if physical examination identifies cardiovascular risk factors, if there is a personal history of cardiovascular disease, or if the child is being admitted as an inpatient. ECG monitoring is advised for haloperidol and mandatory for pimozide (see individual drug monographs and Side-effects above).

Blood pressure monitoring is advised before starting therapy and frequently during dose titration of antipsychotic drugs. Amisulpride, aripiprazole, trifluoperazine, and sulpiride do not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for these drugs.

It is advisable to monitor prolactin concentration at the start of therapy, at 6 months, and then yearly. Children taking antipsychotic drugs not normally associated with symptomatic hyperprolactinaemia (see Choice above) should be considered for prolactin monitoring if they show symptoms of hyperprolactinaemia (such as breast enlargement and galactorrhoea). Regular clinical monitoring of endocrine function should be considered when children are taking an antipsychotic drug known to increase prolactin levels; this includes measuring weight and height, assessing sexual maturation, and monitoring menstrual function.

Children with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year.

Other uses Nausea and vomiting (section 4.6), choreas, motor tics, and intractable hiccup.

Equivalent doses of oral antipsychotic drugs

These equivalences are intended **only** as an approximate guide; individual dosage instructions should **also** be checked; children should be carefully monitored after **any** change in medication

Antipsychotic drug	Daily dose
Chlorpromazine	100 mg
Clozapine	50 mg
Haloperidol	2–3 mg
Pimozide	2 mg
Risperidone	0.5–1 mg
Sulpiride	200 mg
Trifluoperazine	5 mg

Important These equivalences must **not** be extrapolated beyond the max. dose for the drug. Higher doses require careful titration in specialist units and the equivalences shown here may not be appropriate

Dosage

After an initial period of stabilisation, the total daily oral dose of antipsychotic drugs can be given as a single dose in most children. For advice on doses above the *BNF for Children* upper limit, see p. 170.

First-generation antipsychotic drugs

CHLORPROMAZINE HYDROCHLORIDE

Warning Owing to the risk of contact sensitisation, pharmacists, nurses, and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care

Cautions see notes above; also diabetes; children should remain supine, with blood pressure monitoring for 30 minutes after intramuscular injection; dose adjustment may be necessary if smoking started or stopped during treatment

Contra-indications see notes above; hypothyroidism

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

Childhood schizophrenia and other psychoses (under specialist supervision)

• By mouth

Child 1–6 years 500 micrograms/kg every 4–6 hours adjusted according to response (max. 40 mg daily)

Child 6–12 years 10 mg 3 times daily, adjusted according to response (max. 75 mg daily)

Child 12–18 years 25 mg 3 times daily (or 75 mg at night), adjusted according to response, to usual maintenance dose of 75–300 mg daily (but up to 1 g daily may be required)

Relief of acute symptoms of psychoses (under specialist supervision) but see also Cautions and Side-effects

• By deep intramuscular injection

Child 1–6 years 500 micrograms/kg every 6–8 hours (max. 40 mg daily)

Child 6–12 years 500 micrograms/kg every 6–8 hours (max. 75 mg daily)

Child 12–18 years 25–50 mg every 6–8 hours

Chlorpromazine (Non-proprietary) (PoM)

Tablets, chlorpromazine hydrochloride 25 mg, net price 28-tab pack = £2.04; 50 mg, 28-tab pack = £2.15; 100 mg, 28-tab pack = £2.17. Label: 2, 11

Brands include *Chloractil*[®]

Oral solution, chlorpromazine hydrochloride 25 mg/5 mL, net price 150 mL = £2.35; 100 mg/5 mL, 150 mL = £5.50. Label: 2, 11

Injection, chlorpromazine hydrochloride 25 mg/mL, net price 1-mL amp = 60p, 2-mL amp = 63p

Largactil[®] (Sanofi-Aventis) (PoM)

Injection, chlorpromazine hydrochloride 25 mg/mL, net price 2-mL amp = 75p

HALOPERIDOL

Cautions see notes above; also subarachnoid haemorrhage and metabolic disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia; dose adjustment may be necessary if smoking started or stopped during treatment; baseline ECG required before treatment—assess need for further ECGs during treatment on an individual basis

Contra-indications see notes above; QT-interval prolongation (avoid concomitant administration of drugs that prolong QT interval); bradycardia; lesions of the basal ganglia

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy avoid unless benefits outweigh risks; see also notes above

Breast-feeding see notes above

Side-effects see notes above, but less sedating and fewer antimuscarinic or hypotensive symptoms; depression; weight loss; *less commonly* dyspnoea, oedema; *rarely* bronchospasm, hypoglycaemia, and inappropriate antidiuretic hormone secretion; Stevens-Johnson syndrome and toxic epidermal necrolysis also reported

Licensed use not licensed for use in children for nausea and vomiting in palliative care

Indications and dose

Schizophrenia (under specialist supervision)

• By mouth

Child 3–13 years initially 500 micrograms daily in 2–3 divided doses; usual target dose 1–4 mg daily in 2–3 divided doses; max. 6 mg daily in 2–3 divided doses

Child 13–18 years initially 500 micrograms daily in 2–3 divided doses; usual target dose 1–6 mg daily in 2–3 divided doses; max. 10 mg daily in 2–3 divided doses

Childhood behavioural disorders, especially when associated with hyperactivity and aggression, Gilles de la Tourette syndrome (under specialist supervision)

• By mouth

Child 3–13 years 250 micrograms daily in 2–3 divided doses; usual target dose 0.5–3 mg daily in 2–3 divided doses; max. 3 mg daily in 2–3 divided doses

Child 13–18 years 250 micrograms daily in 2–3 divided doses; usual target dose 2–6 mg daily in 2–3 divided doses; max. 6 mg daily in 2–3 divided doses

Nausea and vomiting in palliative care

• By mouth

Child 12–18 years 1.5 mg once daily at night, increased to 1.5 mg twice daily if necessary; max. 5 mg twice daily

• By continuous intravenous or subcutaneous infusion

Child 1 month–12 years 25–85 micrograms/kg over 24 hours

Child 12–18 years 1.5–5 mg over 24 hours

Haloperidol (Non-proprietary) (PoM)

Tablets, haloperidol 500 micrograms, net price 28-tab pack = 91p; 1.5 mg, 28-tab pack = £2.19; 5 mg, 28-tab pack = £3.02; 10 mg, 28-tab pack = £7.81; 20 mg, 28-tab pack = £17.79. Label: 2

Oral liquid, haloperidol 5 mg/5 mL, net price 100-mL pack = £6.41; 10 mg/5 mL, 100-mL pack = £7.10. Label: 2

Injection, haloperidol 5 mg/mL, net price 1-mL amp = 36p

Important When prescribing, dispensing, or administering, check that this injection is the correct preparation—this preparation is usually used in hospital for the rapid control of an *acute episode* and should **not** be confused with depot preparations which are usually used in the community or clinics for *maintenance* treatment

Dozic® (Rosemont) (PoM)

Oral liquid, sugar-free, haloperidol 5 mg/5 mL, net price 100-mL pack = £6.30. Label: 2

Haldol® (Janssen) (PoM)

Oral liquid, sugar-free, haloperidol 10 mg/5 mL, net price 100-mL pack (with pipette) = £4.45. Label: 2

Injection, haloperidol 5 mg/mL, net price 1-mL amp = 36p

Important When prescribing, dispensing, or administering, check that this injection is the correct preparation—this preparation is usually used in hospital for the rapid control of an *acute episode* and should **not** be confused with depot preparations which are usually used in the community or clinics for *maintenance* treatment

Serenace® (TEVA UK) (PoM)

Capsules, green, haloperidol 500 micrograms, net price 30-cap pack = £1.18. Label: 2

LEVOMEPRMAZINE (Methotrimeprazine)

Cautions see notes above; diabetes; children receiving large initial doses should remain supine

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; occasionally raised erythrocyte sedimentation rate occurs; hyperglycaemia also reported

Indications and dose

Restlessness and confusion in palliative care

• By continuous subcutaneous infusion

Child 1–12 years 0.35–3 mg/kg over 24 hours

Child 12–18 years 12.5–200 mg over 24 hours

Nausea and vomiting in palliative care

• By continuous intravenous or subcutaneous infusion

Child 1 month–12 years 100–400 micrograms/kg over 24 hours

Child 12–18 years 5–25 mg over 24 hours

Administration for administration by *subcutaneous infusion* dilute with a suitable volume of Sodium Chloride 0.9%

Nozinan® (Sanofi-Aventis) (PoM)

Tablets, scored, levomepromazine maleate 25 mg, net price 84-tab pack = £20.26. Label: 2

Injection, levomepromazine hydrochloride 25 mg/mL, net price 1-mL amp = £2.01

PERICYAZINE (Pericazine)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above; avoid in renal impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; more sedating; hypotension common when treatment initiated; respiratory depression

Licensed use tablets not licensed for use in children

Indications and dose

Schizophrenia, psychoses (severe mental or behavioural disorders only) (under specialist supervision)

• By mouth

Child 1–12 years initially 500 micrograms daily for 10-kg child, increased by 1 mg for each additional 5 kg to max. total daily dose of 10 mg; dose may be gradually increased according to response but maintenance should not exceed twice initial dose

Child 12–18 years initially 25 mg 3 times daily increased at weekly intervals by steps of 25 mg according to response; usual max. 100 mg 3 times daily; total daily dose may alternatively be given in 2 divided doses

Pericyazine (Non-proprietary) (PoM)

Tablets, pericyazine 2.5 mg, net price 84-tab pack = £15.50; 10 mg, 84-tab pack = £40.00. Label: 2

Syrup, pericyazine 10 mg/5 mL, net price 100-mL pack = £46.00. Label: 2

PERPHENAZINE

Cautions see notes above; hypothyroidism

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; less sedating; dystonia, more frequent (particularly at high dosage); *rarely* systemic lupus erythematosus

Indications and dose

Schizophrenia and other psychoses, mania, short-term adjunctive management of anxiety, severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour (under specialist supervision)

• By mouth

Child 14–18 years initially 4 mg 3 times daily adjusted according to the response; max. 24 mg daily

Fentazin® (AMCo) (PoM)

Tablets, both s/c, perphenazine 2 mg, net price 100-tab pack = £29.09; 4 mg, 100-tab pack = £34.25. Label: 2

PIMOZIDE

Cautions see notes above

ECG monitoring Following reports of sudden unexplained death, an ECG is recommended before treatment. It is also recommended that patients taking pimozide should have an annual ECG (if the QT interval is prolonged, treatment should be reviewed and either withdrawn or dose reduced under close supervision) and that pimozide should not be given with other antipsychotic drugs (including depot preparations), tricyclic antidepressants or other drugs which

prolong the QT interval, such as certain antimalarials, antiarrhythmic drugs and certain antihistamines and should not be given with drugs which cause electrolyte disturbances (especially diuretics)

Contra-indications see notes above; history or family history of congenital QT prolongation; history of arrhythmias

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; less sedating; serious arrhythmias, venous thromboembolism, glycosuria, and *rarely*, hyponatraemia reported

Licensed use not licensed for use in Tourette syndrome

Indications and dose

Schizophrenia (under specialist supervision)

• By mouth

Child 12–18 years initially 1 mg daily, increased according to response in steps of 2–4 mg at intervals of not less than 1 week; usual dose range 2–20 mg daily

Tourette syndrome (under specialist supervision)

• By mouth

Child 2–12 years 1–4 mg daily

Child 12–18 years 2–10 mg daily

Orap® (Janssen) (PoM)

Tablets, scored, green, pimozide 4 mg, net price 100-tab pack = £40.31. Label: 2

SULPIRIDE

Cautions see notes above; also excited, agitated, or aggressive children (even low doses may aggravate symptoms)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also hepatitis and venous thromboembolism

Licensed use not licensed for use in Tourette syndrome

Indications and dose

Schizophrenia (under specialist supervision)

• By mouth

Child 14–18 years 200–400 mg twice daily; max. 800 mg daily in predominantly negative symptoms, dose increased to max. 2.4 g daily in mainly positive symptoms

Tourette syndrome (under specialist supervision)

• By mouth

Child 2–12 years 50–400 mg twice daily

Child 12–18 years 100–400 mg twice daily

Sulpiride (Non-proprietary) (PoM)

Tablets, sulpiride 200 mg, net price 30-tab pack = £5.28; 56-tab pack = £6.46; 400 mg, 30-tab pack = £18.80. Label: 2

Dolmatil® (Sanofi-Aventis) (PoM)

Tablets, both scored, sulphuride 200 mg, net price 100-tab pack = £6.00; 400 mg (f/c), 100-tab pack = £19.00. Label: 2

Sulpur® (Rosemont) (PoM)

Oral solution, sugar-free, lemon- and aniseed-flavoured, sulphuride 200 mg/5 mL, net price 150 mL = £25.38. Label: 2

TRIFLUOPERAZINE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; extrapyramidal symptoms more frequent, especially at doses exceeding 6 mg daily; anorexia; muscle weakness

Indications and dose

Schizophrenia and other psychoses, short-term adjunctive management of psychomotor agitation, excitement and violent or dangerously impulsive behaviour (under specialist supervision)

- By mouth

Child 12–18 years initially 5 mg twice daily, increased by 5 mg daily after 1 week, then at intervals of 3 days, according to response

Short-term adjunctive management of severe anxiety (under specialist supervision)

- By mouth

Child 3–6 years up to 500 micrograms twice daily

Child 6–12 years up to 2 mg twice daily

Child 12–18 years 1–2 mg twice daily, increased if necessary to 3 mg twice daily

Antiemetic section 4.6

Trifluoperazine (Non-proprietary) (PoM)

Tablets, trifluoperazine (as hydrochloride) 1 mg, net price 112-tab pack = £7.22; 5 mg, 112-tab pack = £4.65. Label: 2

Oral solution, trifluoperazine (as hydrochloride) 1 mg/5 mL, net price 200-mL pack = £32.86; 5 mg/5 mL, 150-mL pack = £25.50. Label: 2

Stelazine® (AMCo) (PoM)

Tablets, blue, f/c, trifluoperazine (as hydrochloride) 1 mg, net price 112-tab pack = £4.11; 5 mg, 112-tab pack = £5.87. Label: 2

Second-generation antipsychotic drugs**AMISULPRIDE**

Cautions see notes above

Contra-indications see notes above; prolactin-dependent tumours; prepubertal children

Renal impairment halve dose if estimated glomerular filtration rate 30–60 mL/minute/1.73 m²; use one-third dose if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; no information available if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy avoid

Breast-feeding avoid—no information available

Side-effects see notes above; also anxiety; *less commonly* bradycardia

Licensed use not licensed for use in children under 18 years

Indications and dose

Acute psychotic episode (under specialist supervision)

- By mouth

Child 15–18 years 200–400 mg twice daily adjusted according to response; max. 1.2 g daily

Predominantly negative symptoms (under specialist supervision)

- By mouth

Child 15–18 years 50–300 mg daily

Amisulpride (Non-proprietary) (PoM)

Tablets, amisulpride 50 mg, net price 60-tab pack = £3.84; 100 mg, 60-tab pack = £5.91; 200 mg, 60-tab pack = £9.89; 400 mg, 60-tab pack = £41.36. Label: 2

Solian® (Sanofi-Aventis) (PoM)

Tablets, amisulpride 50 mg, net price 60-tab pack = £22.76; 100 mg, 60-tab pack = £35.29; 200 mg, 60-tab pack = £58.99, 400 mg, 60-tab pack = £117.97. Label: 2

Solution, 100 mg/mL, net price 60 mL (caramel flavour) = £33.76. Label: 2

ARIPIRAZOLE

Cautions see notes above; cerebrovascular disease

Contra-indications see notes above

Hepatic impairment use with caution in severe impairment

Pregnancy see Pregnancy notes, p. 172; also use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—present in milk

Side-effects see notes above; hypersalivation, anxiety, drowsiness, malaise; *less commonly* depression, dry mouth; *also reported* anorexia, oropharyngeal spasm, laryngospasm, respiratory disorders (including infection), hepatitis, pancreatitis, bradycardia, pathological gambling, suicidal ideation, hyponatraemia, urinary disorders, myalgia, rhabdomyolysis, oedema, sweating, alopecia

Indications and dose

Treatment of mania (under specialist supervision)

- By mouth

Child 13–18 years initially 2 mg once daily for 2 days, increased to 5 mg once daily for 2 days, thereafter increased to usual dose of 10 mg once daily; further increased if necessary in steps of 5 mg to max. 30 mg daily, but see also note below; max. duration of treatment 12 weeks; for dose adjustments due to concomitant use of interacting drugs, consult product literature

Important Increased incidence of side-effects associated with doses of 30 mg daily; doses above 10 mg daily should only be used in exceptional cases and with close clinical monitoring

Schizophrenia (under specialist supervision)• **By mouth**

Child 15–18 years initially 2 mg once daily for 2 days, increased to 5 mg once daily for 2 days, thereafter increased to 10 mg once daily; further increased if necessary in steps of 5 mg to max. 30 mg daily; for dose adjustments due to concomitant use of interacting drugs, consult product literature

Abilify® (Otsuka) ▼ (PoM)

Tablets, aripiprazole 5 mg (blue), net price 28-tab pack = £96.04; 10 mg (pink), 28-tab pack = £96.04; 15 mg (yellow), 28-tab pack = £96.04; 30 mg (pink), 28-tab pack = £192.08. Label: 2

Orodispersible tablets, aripiprazole 10 mg (pink), net price 28-tab pack = £96.04; 15 mg (yellow), 28-tab pack = £96.04. Label: 2, counselling, administration
Excipients include aspartame (section 9.4.1)

Counselling Tablets should be placed on the tongue and allowed to dissolve, or be dispersed in water and swallowed

Oral solution, aripiprazole 1 mg/mL, net price 150 mL with measuring cup = £102.90. Label: 2

Note The Scottish Medicines Consortium, p. 3 has advised (August 2013) that oral aripiprazole (Abilify®) is accepted for restricted use within NHS Scotland for the treatment of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older for a period of up to 12 weeks. It is restricted to initiation and management under the supervision of a child/adolescent psychiatrist.

CLOZAPINE

Cautions see notes above; monitor leucocyte and differential blood counts (see Agranulocytosis, below); susceptibility to angle-closure glaucoma; taper off other antipsychotics before starting; close medical supervision during initiation (risk of collapse because of hypotension and convulsions); dose adjustment may be necessary if smoking started or stopped during treatment

Withdrawal On planned withdrawal reduce dose over 1–2 weeks to avoid risk of rebound psychosis. If abrupt withdrawal necessary observe child carefully

Agranulocytosis Neutropenia and potentially fatal agranulocytosis reported. Leucocyte and differential blood counts must be normal before starting; monitor counts every week for 18 weeks then at least every 2 weeks and if clozapine continued and blood count stable after 1 year at least every 4 weeks (and 4 weeks after discontinuation); if leucocyte count below 3000/mm³ or if absolute neutrophil count below 1500/mm³ discontinue permanently and refer to haematologist. Patients who have a low white blood cell count because of benign ethnic neutropenia may be started on clozapine with the agreement of a haematologist. Avoid drugs which depress leucopoiesis; children (or carers) should report immediately symptoms of infection, especially influenza-like illness

Myocarditis and cardiomyopathy Fatal myocarditis (most commonly in first 2 months) and cardiomyopathy reported.

- Perform physical examination and take full medical history before starting;
- Specialist examination required if cardiac abnormalities or history of heart disease found—clozapine initiated only in absence of severe heart disease and if benefit outweighs risk;
- Persistent tachycardia especially in first 2 months should prompt observation for other indicators for myocarditis or cardiomyopathy;
- If myocarditis or cardiomyopathy suspected clozapine should be stopped and child evaluated urgently by cardiologist;

- Discontinue permanently in clozapine-induced myocarditis or cardiomyopathy

Gastro-intestinal obstruction Reactions resembling gastro-intestinal obstruction reported. Clozapine should be used cautiously with drugs which cause constipation (e.g. antimuscarinic drugs) or in children with history of colonic disease or bowel surgery. Monitor for constipation and prescribe laxative if required

Contra-indications severe cardiac disorders (e.g. myocarditis; see Cautions); history of neutropenia or agranulocytosis (see Cautions); bone-marrow disorders; paralytic ileus (see Cautions); alcoholic and toxic psychoses; history of circulatory collapse; drug intoxication; coma or severe CNS depression; uncontrolled epilepsy

Hepatic impairment monitor hepatic function regularly; avoid in symptomatic or progressive liver disease or hepatic failure

Renal impairment avoid in severe impairment

Pregnancy see Pregnancy notes, p. 172; use with caution

Breast-feeding avoid

Side-effects see notes above; also constipation (see Cautions), hypersalivation, anorexia, speech disorders, malaise, urinary incontinence; *less commonly* agranulocytosis (**important**: see Cautions); *rarely* dysphagia, hepatitis, pancreatitis, circulatory collapse, myocarditis (**important**: see Cautions), pericarditis, pulmonary aspiration, pneumonia; *very rarely* parotid gland enlargement, intestinal obstruction (see Cautions), cardiomyopathy (**important**: see Cautions), myocardial infarction, respiratory depression, obsessive compulsive disorder, interstitial nephritis, hypertriglyceridaemia, hypercholesterolaemia; *also reported* hepatic disorders and failure, renal failure, muscle disorders

Licensed use not licensed for use in children under 16 years

Indications and dose

Schizophrenia in children unresponsive to, or intolerant of, conventional antipsychotic drugs (under specialist supervision)

• **By mouth**

Child 12–18 years 12.5 mg once or twice on first day then 25–50 mg on second day then increased gradually (if well tolerated) in steps of 25–50 mg daily over 14–21 days up to 300 mg daily in divided doses (larger dose at night, up to 200 mg daily may be taken as a single dose at bedtime); if necessary may be further increased in steps of 50–100 mg once (preferably) or twice weekly; usual dose 200–450 mg daily (max. 900 mg daily)

Note Restarting after interval of more than 2 days, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation)—extreme caution if previous respiratory or cardiac arrest with initial dosing

Clozaril® (Novartis) (PoM)

Tablets, yellow, clozapine 25 mg (scored), net price 28-tab pack = £3.78, 84-tab pack (hosp. only) = £11.33, 100-tab pack (hosp. only) = £13.48; 100 mg, 28-tab pack = £15.09, 84-tab pack (hosp. only) = £45.28, 100-tab pack (hosp. only) = £53.90. Label: 2, 10, patient information leaflet

Note Child, prescriber, and supplying pharmacist must be registered with the Clozaril Patient Monitoring Service—takes several days to do this

Denzapine® (Genus) (PoM)

Tablets, yellow, scored, clozapine 25 mg, net price 84-tab pack = £16.64, 100-tab pack = £19.80; 50 mg, 50-tab pack = £19.80; 100 mg, 84-tab pack = £66.53, 100-tab pack = £79.20; 200 mg, 50-tab pack = £79.20. Label: 2, 10, patient information leaflet

Suspension, clozapine 50 mg/mL, net price 100 mL = £39.60. Label: 2, 10, patient information leaflet, counselling, administration

Counselling Shake well for 90 seconds when dispensing or if visibly settled and stand for 24 hours before use; otherwise shake well for 10 seconds before use

Note May be diluted in water

Note Child, prescriber, and supplying pharmacist must be registered with the Denzapine Patient Monitoring Service—takes several days to do this

Zaponex® (TEVA UK) (PoM)

Tablets, yellow, scored, clozapine 25 mg, net price 84-tab pack = £8.28; 100 mg, 84-tab pack = £33.88. Label: 2, 10, patient information leaflet

Note Child, prescriber, and supplying pharmacist must be registered with the Zaponex Treatment Access System—takes several days to do this

OLANZAPINE

Cautions see notes above; also paralytic ileus, diabetes mellitus (risk of exacerbation or ketoacidosis), low leucocyte or neutrophil count, bone-marrow depression, hyper-eosinophilic disorders, myeloproliferative disease; dose adjustment may be necessary if smoking started or stopped during treatment

Hepatic impairment consider initial dose of 5 mg daily

Renal impairment consider initial dose of 5 mg daily

Pregnancy see Pregnancy notes, p. 172; use only if potential benefit outweighs risk; neonatal lethargy, tremor and hypertonia reported when used in third trimester

Breast-feeding avoid—present in milk

Side-effects see notes above; also increased appetite, hypertriglyceridaemia, hypercholesterolaemia, arthralgia, oedema, malaise; *less commonly* bradycardia, epistaxis, amnesia, alopecia; *rarely* hepatitis, pancreatitis, rhabdomyolysis

Licensed use not licensed for use in children

Indications and dose

Schizophrenia, combination therapy for mania (under specialist supervision)

- By mouth

Child 12–18 years initially 5–10 mg daily adjusted to usual range of 5–20 mg daily; doses greater than 10 mg daily only after reassessment; max. 20 mg daily

Monotherapy for mania (under specialist supervision)

- By mouth

Child 12–18 years 15 mg daily adjusted to usual range of 5–20 mg daily; doses greater than 15 mg only after reassessment; max. 20 mg daily

Note When one or more factors present that might result in slower metabolism (e.g. female gender, non-smoker) consider lower initial dose and more gradual dose increase

Olanzapine (Non-proprietary) (PoM)

Tablets, olanzapine 2.5 mg, net price 28-tab pack = 96p; 5 mg, 28-tab pack = £1.20; 7.5 mg, 56-tab pack = £2.70; 10 mg, 28-tab pack = £1.51; 15 mg, 28-tab pack = £2.08; 20 mg, 28-tab pack = £2.09. Label: 2

Brands include *Zalasta®*

Orodispersible tablets, olanzapine 5 mg, net price 28-tab pack = £2.73; 10 mg, 28-tab pack = £3.43; 15 mg, 28-tab pack = £4.04; 20 mg, 28-tab pack = £5.66. Label: 2, counselling, administration

Counselling Olanzapine orodispersible tablet may be placed on the tongue and allowed to dissolve, or dispersed in water, orange juice, apple juice, milk, or coffee

Zyprexa® (Lilly) (PoM)

Tablets, f/c, olanzapine 2.5 mg, net price 28-tab pack = £21.85; 5 mg, 28-tab pack = £43.70; 7.5 mg, 56-tab pack = £131.10; 10 mg, 28-tab pack = £87.40; 15 mg (blue), 28-tab pack = £119.18; 20 mg (pink), 28-tab pack = £158.90. Label: 2

Orodispersible tablet (*Velotab®*), yellow, olanzapine 5 mg, net price 28-tab pack = £48.07; 10 mg, 28-tab pack = £87.40; 15 mg, 28-tab pack = £131.10; 20 mg, 28-tab pack = £174.79. Label: 2, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling *Velotab®* may be placed on the tongue and allowed to dissolve, or dispersed in water, orange juice, apple juice, milk, or coffee

QUETIAPINE

Cautions see notes above; cerebrovascular disease; children at risk of aspiration pneumonia

Hepatic impairment for *immediate-release tablets*, initially 25 mg daily, increased daily in steps of 25–50 mg

Pregnancy see Pregnancy notes, p. 172; use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid

Side-effects see notes above; also dyspnoea, elevated plasma-triglyceride and -cholesterol concentrations, peripheral oedema, increased appetite, sleep disorders, irritability, dysarthria, asthenia; *less commonly* rhinitis, restless legs syndrome, hyponatraemia, hypothyroidism; *rarely* pancreatitis, hepatitis; *very rarely* inappropriate secretion of antidiuretic hormone, rhabdomyolysis, angioedema, and Stevens-Johnson syndrome; *also reported* suicidal behaviour (particularly on initiation), toxic epidermal necrolysis

Licensed use not licensed for use in children

Indications and dose

Schizophrenia (under specialist supervision)

- By mouth

Child 12–18 years initially 25 mg twice daily adjusted in steps of 25–50 mg according to response; max. 750 mg daily

Treatment of mania in bipolar disorder (under specialist supervision)

- By mouth

Child 12–18 years 25 mg twice daily on day 1, then 50 mg twice daily on day 2, then 100 mg twice daily on day 3, then 150 mg twice daily on day 4, then 200 mg twice daily on day 5; thereafter dose adjusted according to response in steps no greater than 100 mg daily, usual dose 400–600 mg daily in 2 divided doses

Quetiapine (Non-proprietary) (PoM)

Tablets, quetiapine (as fumarate) 25 mg, net price 60-tab pack = £1.44; 100 mg, 60-tab pack = £2.43; 150 mg, 60-tab pack = £2.78; 200 mg, 60-tab pack = £3.26; 300 mg, 60-tab pack = £4.34. Label: 2

Seroquel® (AstraZeneca) (PoM)

Tablets, f/c, quetiapine (as fumarate) 25 mg (peach), net price 60-tab pack = £40.50; 100 mg (yellow), 60-tab pack = £113.10; 150 mg (pale yellow), 60-tab pack = £113.10; 200 mg (white), 60-tab pack = £113.10; 300 mg (white), 60-tab pack = £170.00. Label: 2

■ **Modified release****Quetiapine m/r preparations** (PoM)

Tablets, m/r, quetiapine (as fumarate) 50 mg, net price 60-tab pack = £67.66; 150 mg, 60-tab pack = £113.10; 200 mg 60-tab pack = £113.10; 300 mg, 60-tab pack = £170.00; 400 mg, 60-tab pack = £226.20. Label: 2, 23, 25

Brands include *Seroquel*® XL, *Tenprolid*® XL

Dose

Schizophrenia (under specialist supervision)

● **By mouth**

Child 12–18 years initially 50 mg once daily adjusted in steps of 50 mg daily according to response, usual dose 400–800 mg once daily; max. 800 mg once daily

Note Patients can be switched from immediate-release to modified-release tablets at the equivalent daily dose; to maintain clinical response, dose titration may be required

RISPERIDONE

Cautions see notes above; prolactin-dependent tumours; dehydration; family history of sudden cardiac death (perform ECG); cataract surgery (risk of intra-operative floppy iris syndrome); avoid in acute porphyria (section 9.8.2)

Hepatic impairment initial and subsequent oral doses should be halved

Renal impairment initial and subsequent oral doses should be halved

Pregnancy see Pregnancy notes, p. 172; use only if potential benefit outweighs risk

Breast-feeding use only if potential benefit outweighs risk—small amount present in milk

Side-effects see notes above; also hypertension, respiratory disorders (including infection), epistaxis, appetite changes, sleep disorders, anxiety, depression, malaise, urinary disorders, arthralgia, myalgia, toothache, oedema; *less commonly* hyposaesthesia, paraesthesia, taste disturbances, elevated plasma-triglyceride and -cholesterol concentrations, visual disorders, tinnitus, alopecia; *rarely* intestinal obstruction, pancreatitis, pulmonary embolism, inappropriate antidiuretic hormone secretion, rhabdomyolysis, intra-operative floppy iris syndrome

Licensed use not licensed for use in children for psychosis, mania, or autism

Indications and dose

Acute and chronic psychosis (under specialist supervision)

● **By mouth**

Child 12–18 years 2 mg in 1–2 divided doses on first day then 4 mg in 1–2 divided doses on second day (slower titration appropriate in some children); usual dose range 4–6 mg daily; doses above 10 mg daily only if benefit considered to outweigh risk (max. 16 mg daily)

Short-term monotherapy of mania in bipolar disorder (under specialist supervision)● **By mouth**

Child 12–18 years initially 500 micrograms once daily adjusted in steps of 0.5–1 mg daily according to response; usual dose 2.5 mg daily in 1–2 divided doses, max. 6 mg daily

Short-term treatment (up to 6 weeks) of persistent aggression in conduct disorder (under specialist supervision)● **By mouth**

Child 5–18 years and body-weight under 50 kg initially 250 micrograms once daily increased according to response in steps of 250 micrograms on alternate days; usual dose 500 micrograms daily (up to 750 micrograms once daily has been required)

Child 5–18 years and body-weight over 50 kg initially 500 micrograms once daily increased according to response in steps of 500 micrograms on alternate days; usual dose 1 mg daily (up to 1.5 mg once daily has been required)

Short-term treatment of severe aggression in autism (under specialist supervision)● **By mouth**

Child over 5 years and 15–20 kg 250 micrograms daily increased if necessary after at least 4 days to 500 micrograms daily; thereafter increased by 250 micrograms daily at 2-week intervals to max. 1 mg daily

Child over 5 years and over 20 kg 500 micrograms daily increased if necessary after at least 4 days to 1 mg daily; thereafter increased by 500 micrograms daily at 2-week intervals; max. daily dose 2.5 mg if under 45 kg; max. daily dose 3 mg if over 45 kg

Note Review effectiveness and any side-effects after 3–4 weeks; stop if no response at 6 weeks

Risperidone (Non-proprietary) (PoM)

Tablets, risperidone 500 micrograms, net price 20-tab pack = £1.05; 1 mg, 20-tab pack = 90p, 60-tab pack = £1.23; 2 mg, 60-tab pack = £1.66; 3 mg, 60-tab pack = £1.99; 4 mg, 60-tab pack = £2.20; 6 mg, 28-tab pack = £5.80. Label: 2

Orodispersible tablets, risperidone 0.5 mg, net price 28-tab pack = £23.32; 1 mg, 28-tab pack = £20.61; 2 mg, 28-tab pack = £37.65; 3 mg, 28-tab pack = £33.52; 4 mg, 28-tab pack = £37.19. Label: 2, counselling, administration

Counselling Tablets should be placed on the tongue, allowed to dissolve and swallowed

Liquid, risperidone 1 mg/mL, net price 100-mL pack = £38.43. Label: 2, counselling, use of dose syringe

Note Liquid may be diluted with any non-alcoholic drink, except tea

Risperdal® (Janssen) (PoM)

Tablets, f/c, scored, risperidone 500 micrograms (brown-red), net price 20-tab pack = £5.08; 1 mg (white), 20-tab pack = £8.36, 60-tab pack = £17.56; 2 mg (orange), 60-tab pack = £34.62; 3 mg (yellow), 60-tab pack = £50.91; 4 mg (green), 60-tab pack = £67.20; 6 mg (yellow), 28-tab pack = £67.88. Label: 2

Orodispersible tablets (*Quicklet*®), pink, risperidone 500 micrograms, net price 28-tab pack = £8.23; 1 mg, 28-tab pack = £13.86; 2 mg, 28-tab pack = £26.12; 3 mg, 28-tab pack = £28.99; 4 mg, 28-tab pack = £37.34. Label: 2, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling Tablets should be placed on the tongue, allowed to dissolve and swallowed

Liquid, risperidone 1 mg/mL, net price 100-mL pack = £37.01. Label: 2, counselling, use of dose syringe

Note Liquid may be diluted with any non-alcoholic drink, except tea

4.2.2 Antipsychotic depot injections

There is limited information on the use of antipsychotic depot injections in children and use should be restricted to specialist centres.

4.2.3 Drugs used for mania and hypomania

Antimanic drugs are used in mania to control acute attacks and to prevent recurrence of episodes of mania or hypomania. Long-term treatment of bipolar disorder should continue for at least two years from the last manic episode and up to five years if the patient has risk factors for relapse.

An antidepressant drug (section 4.3) may also be required for the treatment of co-existing depression, but should be avoided in patients with rapid-cycling bipolar disorder, recent history of hypomania, or rapid mood fluctuations.

Benzodiazepines

Use of benzodiazepines (section 4.1) may be helpful in the initial stages of treatment for behavioural disturbance or agitation; they should not be used for long periods because of the risk of dependence.

Antipsychotic drugs

Atypical antipsychotic drugs (normally **olanzapine**, **quetiapine**, or **risperidone**) (section 4.2.1) are useful in acute episodes of mania and hypomania; if the response to antipsychotic drugs is inadequate, lithium or valproate may be added. An antipsychotic drug may be used concomitantly with lithium or valproate in the initial treatment of severe acute mania.

Atypical antipsychotics are the treatment of choice for the long-term management of bipolar disorder in children and adolescents; if the patient has frequent relapses or continuing functional impairment, consider concomitant therapy with lithium or valproate. An atypical antipsychotic that causes less weight gain and does not increase prolactin levels is preferred.

When discontinuing antipsychotics, the dose should be reduced gradually over at least 4 weeks if the child is continuing on other antimanic drugs; if the child is not continuing on other antimanic drugs, or has a history of manic relapse, a withdrawal period of up to 3 months is required.

High doses of haloperidol may be hazardous when used with lithium; irreversible toxic encephalopathy has been reported.

Carbamazepine

Carbamazepine (section 4.8.1) may be used under specialist supervision for the prophylaxis of bipolar disorder (manic-depressive disorder) in children unresponsive to a combination of other prophylactic drugs; it is used in those with rapid-cycling manic-depressive illness (4 or more affective episodes per year). The dose of carbamazepine should not normally be increased if an acute episode of mania occurs. When stopping treatment with carbamazepine, reduce the dose gradually over a period of at least 4 weeks.

Valproate

Valproic acid (as the semisodium salt) is licensed in adults for the treatment of manic episodes associated with bipolar disorder. Sodium valproate (section 4.8.1) is unlicensed for the treatment of bipolar disorder.

Valproate can be used for the prophylaxis of bipolar disorder [unlicensed use]; however, it should not normally be prescribed for women of child-bearing potential. In patients with frequent relapse or continuing functional impairment, consider switching therapy to lithium or an atypical antipsychotic, or adding lithium or an atypical antipsychotic to valproate. If a patient taking valproate experiences an acute episode of mania that is not ameliorated by increasing the valproate dose, consider concomitant therapy with olanzapine, quetiapine, or risperidone. When stopping valproate reduce the dose gradually over at least 4 weeks.

Lithium

Lithium salts are used in the prophylaxis and treatment of mania, in the prophylaxis of bipolar disorder (manic-depressive disorder), and bipolar depression, and as concomitant therapy with antidepressant medication in children who have had an incomplete response to treatment for acute depression in bipolar disorder [unlicensed indication]. It is also used for the treatment of aggressive or self-harming behaviour [unlicensed indication].

The decision to give prophylactic lithium requires specialist advice, and must be based on careful consideration of the likelihood of recurrence in the individual child, and the benefit of treatment weighed against the risks. The full prophylactic effect of lithium may not occur for six to twelve months after the initiation of therapy. An atypical antipsychotic or valproate (given alone or as adjunctive therapy with lithium) are alternative prophylactic treatments in patients who experience frequent relapses or continuing functional impairment. Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Long-term treatment should therefore be undertaken only with careful assessment of risk and benefit, and with monitoring of thyroid function at baseline and every 6 months (more often if there is evidence of deterioration). Renal function should be monitored at baseline and every 6 months thereafter (more often if there is evidence of deterioration or the patient has other risk factors, such as starting ACE inhibitors, NSAIDs, or diuretics). The need for continued therapy should be assessed regularly and children should be

maintained on lithium after 3 to 5 years only if benefit persists.

Serum concentrations Lithium salts have a narrow therapeutic/toxic ratio and should not be prescribed unless facilities for monitoring serum-lithium concentrations are available. Samples should be taken 12 hours after the dose to achieve a serum-lithium concentration of 0.4–1 mmol/litre. A target serum-lithium concentration of 0.8–1 mmol/litre is recommended for acute episodes of mania, and for patients who have previously relapsed or have sub-syndromal symptoms. It is important to determine the optimum range for each individual child. Serum-lithium monitoring should be performed weekly after initiation and after each dose change until concentrations are stable, then every 3 months thereafter. Additional serum-lithium measurements should be made if a child develops significant intercurrent disease or if there is a significant change in a child's sodium or fluid intake.

Overdosage, usually with serum-lithium concentration of over 1.5 mmol/litre, may be fatal and toxic effects include tremor, ataxia, dysarthria, nystagmus, renal impairment, and convulsions. If these potentially hazardous signs occur, treatment should be stopped, serum-lithium concentrations redetermined, and steps taken to reverse lithium toxicity. In mild cases withdraw lithium and ensure adequate hydration and correction of electrolyte imbalance. Use of IV sodium chloride 0.9% should be considered to maintain urine output. A serum-lithium concentration in excess of 2 mmol/litre requires urgent treatment as described under Emergency Treatment of Poisoning, p. 29.

Interactions Lithium toxicity is made worse by sodium depletion, therefore concurrent use of diuretics (particularly thiazides) is hazardous and should be avoided. For other interactions with lithium, see Appendix 1 (lithium).

Withdrawal While there is no clear evidence of withdrawal or rebound psychosis, abrupt discontinuation of lithium increases the risk of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a period of at least 4 weeks (preferably over a period of up to 3 months). Children and carers should be warned of the risk of relapse if lithium is discontinued abruptly. If lithium is stopped or has to be discontinued abruptly, consider changing therapy to an atypical antipsychotic or valproate.

Lithium treatment packs

A lithium treatment pack should be given to patients on initiation of treatment with lithium. The pack consists of a patient information booklet, lithium alert card, and a record book for tracking serum-lithium concentration.

Packs may be purchased from 3M

Tel: 0845 610 1112 nhsforms@mmm.uk.com

may lower seizure threshold); psoriasis (risk of exacerbation); diuretic treatment (risk of toxicity); myasthenia gravis; surgery (section 15.1); avoid abrupt withdrawal (see notes above); **interactions:** Appendix 1 (lithium)

Counselling children and their carers should be advised to report signs and symptoms of lithium toxicity (see above), hypothyroidism, renal dysfunction (including polyuria and polydipsia), and benign intracranial hypertension (persistent headache and visual disturbance); maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake; may impair performance of skilled tasks (e.g. driving, operating machinery); lithium treatment packs are available (see above)

Contra-indications dehydration, low sodium diets, Addison's disease, untreated hypothyroidism, personal or family history of Brugada syndrome, cardiac insufficiency or rhythm disorder

Renal impairment caution in mild to moderate impairment—monitor serum-lithium concentration closely and adjust dose accordingly; avoid in severe impairment

Pregnancy avoid if possible, particularly in the first trimester (risk of teratogenicity, including cardiac abnormalities); dose requirements increased in second and third trimesters (but on delivery, return abruptly to normal); close monitoring of serum-lithium concentration advised (risk of toxicity in neonate); manufacturer advises effective contraception during treatment for women of child bearing potential

Breast-feeding present in milk and risk of toxicity in infant—avoid

Side-effects gastro-intestinal disturbances, gastritis, weight changes, anorexia, oedema, benign intracranial hypertension, Raynaud's phenomena, ECG changes (including arrhythmia, bradycardia, sinus node dysfunction, QT interval prolongation, AV block), cardiomyopathy, hypersalivation, dry mouth, cognitive impairment, hallucinations, extrapyramidal side-effects, fine tremor, speech disorder, vertigo, memory loss, encephalopathy, dysgeusia, malaise, myasthenia gravis, peripheral neuropathy, kidney changes, renal impairment, polydipsia, nephrotic syndrome, nephrogenic diabetes insipidus, electrolyte imbalance, sexual dysfunction, thyroid changes (including hyperthyroidism, hypothyroidism, euthyroid goitre), hyperparathyroidism, parathyroid adenoma, leucocytosis, arthralgia, myalgia, nystagmus, alopecia, psoriasis exacerbation, acneiform eruptions and other skin disorders; signs of intoxication require withdrawal of treatment and include increasing gastro-intestinal disturbances (vomiting, diarrhoea), visual disturbances, polyuria, muscle weakness, fine tremor increasing to coarse tremor, CNS disturbances (confusion and drowsiness increasing to lack of coordination, restlessness, stupor), abnormal reflexes, myoclonus, incontinence, hypernatraemia; with severe **overdosage** (serum-lithium concentration above 2 mmol/litre) seizures; cardiac arrhythmias (including sino-atrial block, bradycardia and first-degree heart block), blood pressure changes, circulatory failure, renal failure, coma and sudden death reported; see also Emergency Treatment of Poisoning, p. 29

Licensed use not licensed for aggressive or self-harming behaviour; not licensed for concomitant therapy with antidepressant medication in children who have had an incomplete response to treatment for acute depression in bipolar disorder; *Camcolit*® brand not licensed for use in children

LITHIUM CARBONATE

Cautions see notes above; assess cardiac, renal and thyroid function before initiating, and thereafter every 6 months on stabilised regimens; cardiac disease; QT-interval prolongation (caution with concomitant use of drugs that prolong the QT interval); review dose as necessary in diarrhoea, vomiting, and intercurrent infection (especially if sweating profusely); may lower seizure threshold (caution with epilepsy, concurrent ECT, concomitant use of drugs and any therapy that

Indications and dose

Treatment and prophylaxis of mania, bipolar disorder, recurrent depression (see also notes above), aggressive or self-mutilating behaviour

- **By mouth**

See under preparations below, adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter; doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

Note Preparations vary widely in bioavailability; changing the preparation requires the same precautions as initiation of treatment

Camcolit® (Norgine) (PoM)

Camcolit 250® tablets, f/c, scored, lithium carbonate 250 mg (Li^+ 6.8 mmol), net price 100-tab pack = £3.22. Label: 10, lithium card, counselling, driving, fluid and salt intake, toxicity symptoms, see above

Camcolit 400® tablets, m/r, f/c, scored, lithium carbonate 400 mg (Li^+ 10.8 mmol), net price 100-tab pack = £4.30. Label: 10, lithium card, 25, counselling, driving, fluid and salt intake, toxicity symptoms, see above

Dose**Treatment**

- **By mouth**

(see above for advice on bioavailability and serum-lithium monitoring)

Child 12–18 years initially 1–1.5 g daily

Prophylaxis

- **By mouth**

(see above for advice on bioavailability and serum-lithium monitoring)

Child 12–18 years initially 300–400 mg daily

Note Camcolit 400® also available as *Lithonate®* (TEVA UK)

Liskonum® (GSK) (PoM)

Tablets, m/r, f/c, scored, lithium carbonate 450 mg (Li^+ 12.2 mmol), net price 60-tab pack = £2.88.

Label: 10, lithium card, 25, counselling, driving, fluid and salt intake, toxicity symptoms, see above

Dose**Treatment**

- **By mouth**

(see above for advice on bioavailability and serum-lithium monitoring)

Child 12–18 years initially 225–675 mg twice daily

Prophylaxis

- **By mouth**

(see above for advice on bioavailability and serum-lithium monitoring)

Child 12–18 years initially 225–450 mg twice daily

LITHIUM CITRATE

Cautions see Lithium Carbonate and notes above

Counselling Children and their carers should be advised to report signs and symptoms of lithium toxicity (see above), hypothyroidism, renal dysfunction (including polyuria and polydipsia), and benign intracranial hypertension (persistent headache and visual disturbance); maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake; may impair performance of skilled tasks (e.g. driving, operating machinery); lithium treatment packs are available (see above)

Contra-indications see Lithium Carbonate

Renal impairment see Lithium Carbonate

Pregnancy see Lithium Carbonate

Breast-feeding see Lithium Carbonate

Side-effects see Lithium Carbonate

Licensed use not licensed for use in children

Indications and dose

See notes above and Lithium Carbonate

- **By mouth**

Adjust to achieve serum-lithium concentration of 0.4–1 mmol/litre as described under Lithium Carbonate above

Note Preparations vary widely in bioavailability; changing the preparation requires the same precautions as initiation of treatment

Li-Liquid® (Rosemont) (PoM)

Oral solution, lithium citrate tetrahydrate 509 mg/5 mL (Li^+ 5.4 mmol/5 mL), yellow, net price 150-mL pack = £5.79; 1.018 g/5 mL (Li^+ 10.8 mmol/5 mL), orange, 150-mL pack = £11.58. Label: 10, lithium card, counselling, driving, fluid and salt intake, toxicity symptoms, see above

Note Lithium citrate tetrahydrate 509 mg is equivalent to lithium carbonate 200 mg

Priadel® (Sanofi-Aventis) (PoM)

Liquid, sugar-free, lithium citrate tetrahydrate 520 mg/5 mL (approx. Li^+ 5.5 mmol/5 mL), net price 150-mL pack = £5.61. Label: 10, lithium card, counselling, driving, fluid and salt intake, toxicity symptoms, see above

Note Lithium citrate tetrahydrate 520 mg is equivalent to lithium carbonate 204 mg

4.3 Antidepressant drugs

4.3.1 Tricyclic antidepressant drugs

4.3.2 Monoamine-oxidase inhibitors

4.3.3 Selective serotonin re-uptake inhibitors

4.3.4 Other antidepressant drugs

Depression in children should be managed by an appropriate specialist and treatment should involve psychological therapy.

The major classes of antidepressant drugs include the tricyclics and related antidepressant drugs (section 4.3.1), the selective serotonin re-uptake inhibitors (SSRIs) (section 4.3.3), and the monoamine oxidase inhibitors (MAOIs).

Antidepressant drugs should not be used routinely in mild depression, and psychological therapy should be considered initially; however, a trial of antidepressant therapy may be considered in cases refractory to psychological treatments or in those associated with psychosocial or medical problems. Drug treatment of mild depression may also be considered in children with a history of moderate or severe depression.

Choice of antidepressant drug should be based on the individual child's requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy.

When drug treatment of depression is considered necessary in children, the SSRIs should be considered first-

line treatment; following a safety and efficacy review, **fluoxetine** is licensed to treat depression in children.

Tricyclic antidepressant drugs should be avoided for the treatment of depression in children.

St John's wort (*Hypericum perforatum*) is a popular herbal remedy on sale to the public for treating mild depression in adults. It should not be used for the treatment of depression in children because St John's wort can induce drug metabolising enzymes and a number of important interactions with conventional drugs, including conventional antidepressants, have been identified (see Appendix 1, St John's wort). Furthermore, the amount of active ingredient varies between different preparations of St John's wort and switching from one to another can change the degree of enzyme induction. If a child stops taking St John's wort, the concentration of interacting drugs may increase, leading to toxicity.

Hyponatraemia and antidepressant therapy

Hyponatraemia (possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants; however, it has been reported more frequently with SSRIs than with other antidepressant drugs. Hyponatraemia should be considered in all children who develop drowsiness, confusion, or convulsions while taking an antidepressant drug.

Suicidal behaviour and antidepressant therapy

The use of antidepressant drugs has been linked with suicidal thoughts and behaviour. Where necessary, children should be monitored for suicidal behaviour, self-harm, and hostility, particularly at the beginning of treatment or if the dose is changed.

Management Children should be reviewed every 1–2 weeks at the start of antidepressant treatment. Treatment should be continued for at least 4 weeks before considering whether to switch antidepressant due to lack of efficacy. In cases of partial response, continue for a further 2–4 weeks. Following remission, antidepressant treatment should be continued at the same dose for at least 6 months. Children with a history of recurrent depression should continue treatment for at least 2 years.

Withdrawal Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in children who have been on long-term maintenance treatment). See also section 4.3.1, and section 4.3.3.

Anxiety Management of *acute anxiety* in children with drug treatment is contentious (section 4.1.2). For *chronic anxiety* (of longer than 4 weeks' duration), it may be appropriate to use an antidepressant drug before a benzodiazepine.

4.3.1 Tricyclic antidepressant drugs

Tricyclic antidepressants are not effective for treating depression in children.

For reference to the role of some tricyclic antidepressant drugs in some forms of *neuralgia*, see section 4.7.3, and in *nocturnal enuresis* in children, see section 7.4.2.

Dosage It is important to use doses that are sufficiently high for effective treatment but not so high as to cause toxic effects. Low doses should be used for initial treatment.

In most children the long half-life of tricyclic antidepressant drugs allows **once-daily** administration, usually at night; the use of modified-release preparations is therefore unnecessary.

Cautions Tricyclic antidepressant drugs should be used with caution in children with cardiovascular disease (see also Contra-indications, below); because of the risk of arrhythmias, children with concomitant conditions such as hyperthyroidism and pheochromocytoma should be treated with care. Care is also needed in children with epilepsy and diabetes.

Tricyclic antidepressant drugs have antimuscarinic activity, and therefore caution is needed in children with chronic constipation, urinary retention, or those with a susceptibility to angle-closure glaucoma. Tricyclic antidepressant drugs should be used with caution in children with a significant risk of suicide, or a history of psychosis or bipolar disorder, because antidepressant therapy may aggravate these conditions; treatment should be stopped if the child enters a manic phase.

Skilled tasks Drowsiness may affect the performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Contra-indications Tricyclic antidepressants are contra-indicated in arrhythmias (particularly heart block), and in the manic phase of bipolar disorder. Avoid treatment with tricyclic antidepressant drugs in acute porphyria (section 9.8.2).

Hepatic impairment The sedative effects of tricyclic antidepressant drugs are increased in children with hepatic impairment. They should be avoided in severe liver disease.

Breast-feeding The amount of tricyclic antidepressants secreted into breast milk is too small to be harmful (but see Doxepin, p. 185).

Side-effects Arrhythmias and heart block occasionally follow the use of tricyclic antidepressants, particularly amitriptyline, and may be a factor in the sudden death of children with cardiac disease; other cardiovascular side-effects include postural hypotension, tachycardia, and ECG changes.

Central nervous system side-effects are common, and include anxiety, dizziness, agitation, confusion, sleep disturbances, irritability, and paraesthesia; drowsiness is associated with some of the tricyclic antidepressants. Convulsions, hallucinations, delusions, mania, and hypomania may occur (see also under Cautions, above), and, rarely, extrapyramidal symptoms including tremor and dysarthria.

Antimuscarinic side-effects include dry mouth, blurred vision (*very rarely* precipitation of angle-closure glaucoma), constipation (*rarely* leading to paralytic ileus), and urinary retention.

Endocrine effects include breast enlargement, galactorrhoea, and gynaecomastia. Sexual dysfunction may occur. Changes in blood sugar, increased appetite, and weight gain can accompany treatment with tricyclic antidepressant drugs, but anorexia and weight loss are also seen. Hepatic and haematological reactions may occur. Hyponatraemia has been associated with antidepressant treatment (see Hyponatraemia and Antidepressant Therapy, p. 184). Other class side-effects include nausea, vomiting, taste disturbance, tinnitus, rash, urticaria, pruritus, photosensitivity, alopecia, and sweating.

Neuroleptic malignant syndrome (section 4.2.1) may, *very rarely*, occur in the course of antidepressant drug treatment.

Suicidal behaviour has been linked with antidepressant drugs (see p. 184).

Overdosage Limited quantities of tricyclic antidepressant drugs should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage. In particular, overdosage with **amitriptyline** is associated with a relatively high rate of fatality. For advice on overdosage see Emergency Treatment of Poisoning, p. 28.

Withdrawal Withdrawal symptoms include influenza-like symptoms (chills, myalgia, sweating, headache, nausea), insomnia, vivid dreams, and may occasionally include movement disorders and mania. If possible tricyclic antidepressant drugs should be withdrawn slowly (see also section 4.3).

AMITRIPTYLINE HYDROCHLORIDE

Cautions see notes above; **interactions:** Appendix 1 (antidepressants, tricyclic)

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy use only if potential benefit outweighs risk

Breast-feeding see notes above

Side-effects see notes above; also abdominal pain, stomatitis, palpitation, oedema, hypertension, restlessness, fatigue, mydriasis, and increased intra-ocular pressure; **overdosage:** see Emergency Treatment of Poisoning, p. 28 (high rate of fatality—see Overdosage, above)

Licensed use not licensed for use in neuropathic pain

Indications and dose

Depression (but see notes above)

• By mouth

Child 16–18 years 10–25 mg 3 times daily (total daily dose may alternatively be given as a single dose at bedtime) increased gradually as necessary to 150–200 mg daily

Neuropathic pain

• By mouth

Child 2–12 years initially 200–500 micrograms/kg (max. 10 mg) once daily at night, increased if necessary; max. 1 mg/kg twice daily on specialist advice

Child 12–18 years initially 10 mg once daily at night, increased gradually if necessary to usual dose 75 mg at night; higher doses on specialist advice

Amitriptyline (Non-proprietary) (PoM)

Tablets, coated, amitriptyline hydrochloride 10 mg, net price 28 = 83p; 25 mg, 28 = 84p; 50 mg, 28 = 92p. Label: 2

Oral solution, amitriptyline hydrochloride 25 mg/5 mL, net price 150 mL = £17.22; 50 mg/5 mL, 150 mL = £18.21. Label: 2

DOXEPIN

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment use with caution

Pregnancy use with caution—limited information available

Breast-feeding see notes above; accumulation of doxepin metabolite may cause sedation and respiratory depression

Side-effects see notes above; also abdominal pain, stomatitis, diarrhoea, flushing, and oedema

Indications and dose

Depressive illness, particularly where sedation is required (but see notes above)

• By mouth

Child 12–18 years initially 75 mg daily in divided doses or as a single dose at bedtime, adjusted according to response; usual maintenance 25–300 mg daily (doses above 100 mg given in 3 divided doses)

Sinepin® (Marlbrough) (PoM)

Capsules, doxepin (as hydrochloride) 25 mg (blue/red), net price 28-cap pack = £3.77; 50 mg (blue), 28-cap pack = £5.71. Label: 2

IMIPRAMINE HYDROCHLORIDE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment use with caution in severe impairment

Pregnancy colic, tachycardia, dyspnoea, irritability, muscle spasms, respiratory depression, and withdrawal symptoms reported in neonates when used in third trimester

Breast-feeding see notes above

Side-effects see notes above; also palpitation, flushing, restlessness, headache, fatigue; *very rarely* abdominal pain, stomatitis, diarrhoea, hypertension, oedema, cardiac decompensation, allergic alveolitis, aggression, myoclonus, peripheral vasospasm, and mydriasis

Licensed use not licensed for use for attention deficit hyperactivity disorder

Indications and dose**Nocturnal enuresis**

- By mouth

Child 6–8 years 25 mg at bedtime

Child 8–11 years 25–50 mg at bedtime

Child 11–18 years 50–75 mg at bedtime

Note Initial period of treatment (including gradual withdrawal) 3 months—full physical examination before further course, see also section 7.4.2

Attention deficit hyperactivity disorder (under specialist supervision)

- By mouth

Child 6–18 years 10–30 mg twice daily

Imipramine (Non-proprietary) (PoM)

Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.19; 25 mg, 28-tab pack = £1.26. Label: 2

Oral solution, imipramine hydrochloride 25 mg/5 mL, net price 150-mL = £31.25. Label: 2

NORTRIPTYLINE

Cautions see notes above; manufacturer advises plasma-nortriptyline concentration monitoring if dose above 100 mg daily, but evidence of practical value uncertain

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy use only if potential benefit outweighs risk

Breast-feeding see notes above

Side-effects see notes above; also abdominal pain, stomatitis, diarrhoea, hypertension, oedema, flushing, restlessness, fatigue, and mydriasis

Indications and dose**Depression** (but see notes above)

- By mouth

Child 12–18 years low dose initially increased as necessary to 30–50 mg daily in divided doses or as a single dose (max. 150 mg daily)

Allegron® (King) (PoM)

Tablets, nortriptyline (as hydrochloride) 10 mg, net price 100-tab pack = £12.06; 25 mg (orange, scored), 100-tab pack = £24.02. Label: 2

Depressive illness in children and adolescents

The balance of risks and benefits for the treatment of depressive illness in individuals under 18 years is considered unfavourable for the SSRIs **citalopram**, **escitalopram**, **paroxetine**, and **sertraline**, and for **mirtazapine** and **venlafaxine**. Clinical trials have failed to show efficacy and have shown an increase in harmful outcomes. However, it is recognised that specialists may sometimes decide to use these drugs in response to individual clinical need; children and adolescents should be monitored carefully for suicidal behaviour, self-harm or hostility, particularly at the beginning of treatment. Only **fluoxetine** has been shown in clinical trials to be effective for treating depressive illness in children and adolescents. However, it is possible that, in common with the other SSRIs, it is associated with a small risk of self-harm and suicidal thoughts. Overall, the balance of risks and benefits for fluoxetine in the treatment of depressive illness in individuals under 18 years is considered favourable, but children and adolescents must be carefully monitored as above.

Cautions SSRIs should be used with caution in children with epilepsy (avoid if poorly controlled, discontinue if convulsions develop), cardiac disease, diabetes mellitus, susceptibility to angle-closure glaucoma, a history of mania or bleeding disorders (especially gastro-intestinal bleeding), and if used together with other drugs that increase the risk of bleeding. They should also be used with caution in those receiving concurrent electroconvulsive therapy (prolonged seizures reported with fluoxetine). SSRIs may also impair performance of skilled tasks (e.g. driving, operating machinery). **Interactions:** Appendix 1 (antidepressants, SSRI).

Withdrawal Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, electric shock sensation in the head, neck, and spine, tinnitus, sleep disturbances, fatigue, influenza-like symptoms, and sweating are the most common features of abrupt withdrawal of an SSRI or marked reduction of the dose; palpitation and visual disturbances can occur less commonly. The dose should be tapered over at least a few weeks to avoid these effects. It may be necessary to withdraw treatment over a longer period; consider obtaining specialist advice if symptoms persist.

Contra-indications SSRIs should not be used if the child enters a manic phase.

Pregnancy Manufacturers advise that SSRIs should not be used during pregnancy unless the potential benefit outweighs the risk. There is a small increased risk of congenital heart defects when SSRIs are taken during early pregnancy. If SSRIs are used during the third trimester there is a risk of neonatal withdrawal symptoms, and persistent pulmonary hypertension in the newborn has been reported.

Side-effects SSRIs are less sedating and have fewer antimuscarinic and cardiotoxic effects than tricyclic antidepressant drugs (section 4.3.1). Side-effects of the SSRIs include gastro-intestinal effects (dose-related and fairly common—include nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation), anorexia with weight loss (increased appetite and weight gain also reported) and hypersensitivity reactions including rash (consider discontinuation—may be sign of impending

4.3.2 Monoamine-oxidase inhibitors (MAOIs)

Classification not used in *BNF for Children*.

4.3.3 Selective serotonin re-uptake inhibitors

Citalopram, **fluoxetine**, **fluvoxamine**, and **sertraline** selectively inhibit the re-uptake of serotonin (5-hydroxytryptamine, 5-HT); they are termed selective serotonin re-uptake inhibitors (SSRIs).

serious systemic reaction, possibly associated with vasculitis), urticaria, angioedema, anaphylaxis, arthralgia, myalgia and photosensitivity; other side-effects include dry mouth, nervousness, anxiety, headache, insomnia, tremor, dizziness, asthenia, hallucinations, drowsiness, convulsions (see Cautions above), galactorrhoea, sexual dysfunction, urinary retention, sweating, hypomania or mania (see Cautions above), movement disorders and dyskinesias, visual disturbances, hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 184), and bleeding disorders including ecchymoses and purpura. Suicidal behaviour has been linked with antidepressants, see p. 184. Angle-closure glaucoma may very rarely be precipitated by treatment with SSRIs.

Overdosage for advice on overdosage with SSRIs see Emergency treatment of poisoning, p. 28

CITALOPRAM

Cautions see notes above; susceptibility to QT-interval prolongation

Contra-indications see notes above; QT-interval prolongation (avoid concomitant administration of drugs that prolong QT-interval)

Hepatic impairment use doses at lower end of range; for *tablets* up to max. 20 mg; for *oral solution* up to max. 16 mg

Renal impairment no information available for estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Pregnancy see notes above

Breast-feeding present in milk—use with caution

Side-effects see notes above; also hepatitis, palpitation, tachycardia, oedema, bradycardia, postural hypotension, haemorrhage, QT-interval prolongation, coughing, yawning, confusion, impaired concentration, aggression, malaise, amnesia, migraine, paraesthesia, abnormal dreams, euphoria, mydriasis, taste disturbance, increased salivation, rhinitis, tinnitus, polyuria, micturition disorders, hypokalaemia, and pruritus

Licensed use not licensed for use in children

Indications and dose

Major depression (but see Depressive Illness in Children and Adolescents, above)

• By mouth as tablets

Child 12–18 years initially 10 mg once daily increased if necessary to 20 mg once daily over 2–4 weeks; max. 40 mg once daily

• By mouth as oral drops

Child 12–18 years initially 8 mg once daily increased if necessary to 16 mg once daily over 2–4 weeks; max. 32 mg once daily

Citalopram (Non-proprietary) (PoM)

Tablets, citalopram (as hydrobromide) 10 mg, net price 28-tab pack = 86p; 20 mg, 28-tab pack = 88p; 40 mg, 28-tab pack = 99p. Counselling, driving

Oral drops, citalopram (as hydrochloride) 40 mg/mL, net price 15-mL pack = £7.05. Counselling, driving, administration

Note 4 drops (8 mg) can be considered equivalent in therapeutic effect to 10-mg tablet

Ciprami® (Lundbeck) (PoM)

Tablets, f/c, citalopram (as hydrobromide) 20 mg (scored), net price 28-tab pack = £8.95. Counselling, driving

Oral drops, sugar-free, citalopram (as hydrochloride) 40 mg/mL, net price 15-mL pack = £10.08. Counselling, driving, administration

Note 4 drops (8 mg) can be considered equivalent in therapeutic effect to 10-mg tablet

Mix with water, orange juice, or apple juice before taking

FLUOXETINE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment reduce dose or increase dose interval

Pregnancy see notes above

Breast-feeding present in breast milk, avoid

Side-effects see notes above; also dysphagia, vasodilatation, hypotension, flushing, palpitation, pharyngitis, dyspnoea, chills, taste disturbance, sleep disturbances, malaise, euphoria, confusion, yawning, impaired concentration, changes in blood sugar, alopecia, urinary frequency, haemorrhage, pulmonary inflammation and fibrosis, hepatitis, toxic epidermal necrolysis, priapism, neuroleptic malignant syndrome-like event

Indications and dose

Major depression

• By mouth

Child 8–18 years 10 mg daily increased after 1–2 weeks if necessary, max. 20 mg daily

Long duration of action Consider the long half-life of fluoxetine when adjusting dosage (or in overdosage)

Note Daily dose may be administered as a single or divided dose

Fluoxetine (Non-proprietary) (PoM)

Capsules, fluoxetine (as hydrochloride) 20 mg, net price 30-cap pack = 99p; 60 mg, 30-cap pack = £29.97. Counselling, driving

Brands include *Oxactin®*

Liquid, fluoxetine (as hydrochloride) 20 mg/5 mL, net price 70 mL = £4.43. Counselling, driving

Brands include *Prozep®*

Prozac® (Lilly) (PoM)

Capsules, fluoxetine (as hydrochloride) 20 mg (green/yellow), net price 30-cap pack = £1.50. Counselling, driving

Liquid, fluoxetine (as hydrochloride) 20 mg/5 mL, net price 70 mL = £11.12. Counselling, driving

FLUVOXAMINE MALEATE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment start with low dose

Renal impairment start with low dose

Pregnancy see notes above

Breast-feeding present in milk—avoid

Side-effects see notes above; palpitation, tachycardia, malaise; *less commonly* postural hypotension, confusion, ataxia; *rarely* abnormal liver function (usually symptomatic—discontinue treatment); *also reported* paraesthesia, taste disturbance, neuroleptic malignant syndrome-like event

Indications and dose**Obsessive-compulsive disorder**

• By mouth

Child 8–18 years initially 25 mg daily increased if necessary in steps of 25 mg every 4–7 days according to response (total daily doses above 50 mg in 2 divided doses); max. 100 mg twice daily

Note If no improvement in obsessive-compulsive disorder within 10 weeks, treatment should be reconsidered

Fluvoxamine (Non-proprietary) (PoM)

Tablets, fluvoxamine maleate 50 mg, net price 60-tab pack = £16.62; 100 mg, 30-tab pack = £16.62.

Counselling, driving

Faverin® (Abbott Healthcare) (PoM)

Tablets, f/c, scored, fluvoxamine maleate 50 mg, net price 60-tab pack = £17.10; 100 mg, 30-tab pack = £17.10. Counselling, driving

SERTRALINE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment reduce dose or increase dose interval in mild or moderate impairment; avoid in severe impairment

Renal impairment use with caution

Pregnancy see notes above

Breast-feeding not known to be harmful but consider discontinuing breast-feeding

Side-effects see notes above; pancreatitis, hepatitis, jaundice, liver failure, stomatitis, palpitation, hypertension, hypercholesterolaemia, tachycardia, postural hypotension, bronchospasm, amnesia, paraesthesia, aggression, hypoglycaemia, hypothyroidism, hyperprolactinaemia, urinary incontinence, menstrual irregularities, leucopenia, and tinnitus also reported

Licensed use not licensed for use in children for depression

Indications and dose**Obsessive-compulsive disorder**

• By mouth

Child 6–12 years initially 25 mg daily increased to 50 mg daily after 1 week, further increased if necessary in steps of 50 mg at intervals of at least 1 week; max. 200 mg daily

Child 12–18 years initially 50 mg daily increased if necessary in steps of 50 mg over several weeks; max. 200 mg daily

Major depression (but see Depressive Illness in Children and Adolescents, above)

• By mouth

Child 12–18 years initially 50 mg once daily increased if necessary in steps of 50 mg daily at intervals of at least a week; max. 200 mg once daily

Sertraline (Non-proprietary) (PoM)

Tablets, sertraline (as hydrochloride) 50 mg, net price 28-tab pack = £2.09; 100 mg, 28-tab pack = £2.98. Counselling, driving

Lustral® (Pfizer) (PoM)

Tablets, both f/c, sertraline (as hydrochloride) 50 mg (scored), net price 28-tab pack = £17.82; 100 mg, 28-tab pack = £29.16. Counselling, driving

4.3.4 Other antidepressant drugs

Classification not used in *BNF for Children*.

4.4 CNS stimulants and other drugs for attention deficit hyperactivity disorder

CNS stimulants should be prescribed for children with severe and persistent symptoms of *attention deficit hyperactivity disorder* (ADHD), when the diagnosis has been confirmed by a specialist; children with moderate symptoms of ADHD can be treated with CNS stimulants when psychological interventions have been unsuccessful or are unavailable. Prescribing of CNS stimulants may be continued by general practitioners under a shared-care arrangement. Treatment of ADHD often needs to be continued into adolescence, and may need to be continued into adulthood.

Drug treatment of ADHD should be part of a comprehensive treatment programme. The choice of medication should take into consideration co-morbid conditions (such as tic disorders, Tourette syndrome, and epilepsy), the adverse effect profile, potential for drug misuse, tolerance and dependence; and preferences of the child and carers. **Methylphenidate** and **atomoxetine** are used for the management of ADHD; **dexamfetamine** and **lisdexamfetamine** are an alternative in children who do not respond to these drugs. Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

NICE guidance**Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) (March 2006)**

Methylphenidate, atomoxetine and dexamfetamine are recommended, within their licensed indications, as options for the management of ADHD in children and adolescents.

www.nice.org.uk/TA98

The need to continue drug treatment for ADHD should be reviewed at least annually. This may involve suspending treatment.

A tricyclic antidepressant such as **imipramine** (section 4.3.1) is sometimes used in the treatment of ADHD; it should not be prescribed concomitantly with a CNS stimulant.

Dexamfetamine and methylphenidate [both unlicensed] are also used to treat narcolepsy.

ATOMOXETINE

Cautions see notes above; also cardiovascular disease including hypertension and tachycardia (avoid in severe cardiovascular disease); structural cardiac abnormalities; QT-interval prolongation (avoid concomitant use of drugs that prolong QT interval); cerebrovascular disease (avoid in severe cerebrovascular disease); psychosis or mania; monitor for appearance or worsening of anxiety, depression or

tics; history of seizures; aggressive behaviour, hostility, or emotional lability; susceptibility to angle-closure glaucoma; **interactions:** Appendix 1 (atomoxetine)

Hepatic disorders Following rare reports of hepatic disorders, children and carers should be advised of the risk and be told how to recognise symptoms; prompt medical attention should be sought in case of abdominal pain, unexplained nausea, malaise, darkening of the urine or jaundice

Suicidal ideation Following reports of suicidal thoughts and behaviour, children and carers should be informed about the risk and told to report clinical worsening, suicidal thoughts or behaviour, irritability, agitation, or depression

Contra-indications pheochromocytoma

Hepatic impairment halve dose in moderate impairment; quarter dose in severe impairment; see also Hepatic Disorders above

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk

Breast-feeding avoid—present in milk in animal studies

Side-effects anorexia, dry mouth, nausea, vomiting, abdominal pain, constipation, dyspepsia, flatulence, palpitation, tachycardia, increased blood pressure, flushing, sleep disturbances, dizziness, headache, malaise, lethargy, drowsiness, anxiety, depression, irritability, taste disturbances, paraesthesia, tremor, chills, urinary dysfunction, prostatitis, sexual dysfunction, mydriasis, dermatitis, rash, sweating; *less commonly* QT-interval prolongation, syncope, suicidal ideation (see Suicidal ideation, above), aggression, hostility, emotional lability, tics, psychosis, hypoaesthesia, cold extremities, menstrual disturbances, muscle spasms, pruritus; *rarely* seizures, Raynaud's phenomenon; *very rarely* hepatic disorders (see Hepatic disorders, above), angle-closure glaucoma

Licensed use doses above 100 mg daily not licensed

Indications and dose

Attention deficit hyperactivity disorder initiated by specialist

• By mouth

Child over 6 years (body-weight under 70 kg)

initially 500 micrograms/kg daily for 7 days, increased according to response; usual maintenance dose 1.2 mg/kg daily, but may be increased to 1.8 mg/kg daily (max. 120 mg daily) under the direction of a specialist

Child over 6 years (body-weight over 70 kg)

initially 40 mg daily for 7 days, increased according to response; usual maintenance dose 80 mg daily, but may be increased to max. 120 mg daily under the direction of a specialist

Note Total daily dose may be given *either* as a single dose in the morning *or* in 2 divided doses with last dose no later than early evening

Strattera® (Lilly) (PoM)

Capsules, atomoxetine (as hydrochloride) 10 mg (white), net price 7-cap pack = £15.62, 28-cap pack = £62.46; 18 mg (gold/white), 7-cap pack = £15.62, 28-cap pack = £62.46; 25 mg (blue/white), 7-cap pack = £15.62, 28-cap pack = £62.46; 40 mg (blue), 7-cap pack = £15.62, 28-cap pack = £62.46; 60 mg (blue/gold), 28-cap pack = £62.46; 80 mg (brown/white), 28-cap pack = £83.28; 100 mg (brown), 28-cap pack = £83.28. Label: 3

DEXAMFETAMINE SULFATE

(Dexamphetamine sulfate)

Cautions see notes above; also anorexia; mild hypertension (contra-indicated if moderate or severe); psychosis or bipolar disorder; monitor for aggressive behaviour or hostility during initial treatment; history of epilepsy (discontinue if seizures occur); tics and Tourette syndrome (use with caution)—discontinue if tics occur; susceptibility to angle-closure glaucoma; avoid abrupt withdrawal; data on safety and efficacy of long-term use not complete; acute porphyria (see section 9.8.2); **interactions:** Appendix 1 (sympathomimetics)

Growth restriction Monitor height and weight as growth restriction may occur during prolonged therapy (drug-free periods may allow catch-up in growth but withdraw slowly to avoid inducing depression or renewed hyperactivity)

Contra-indications cardiovascular disease including moderate to severe hypertension, structural cardiac abnormalities, hyperexcitability or agitated states, hyperthyroidism, history of drug or alcohol abuse

Skilled tasks May affect performance of skilled tasks (e.g. driving); effects of alcohol unpredictable

Renal impairment use with caution

Pregnancy avoid (retrospective evidence of uncertain significance suggesting possible embryotoxicity)

Breast-feeding significant amount in milk—avoid

Side-effects nausea, diarrhoea, dry mouth, abdominal cramps, anorexia (increased appetite also reported), weight loss, taste disturbance, ischaemic colitis, palpitation, tachycardia, chest pain, hypertension, hypotension, cardiomyopathy, myocardial infarction, cardiovascular collapse, cerebral vasculitis, stroke, headache, restlessness, depression, hyperreflexia, hyperactivity, impaired concentration, ataxia, anxiety, aggression, dizziness, confusion, sleep disturbances, dysphoria, euphoria, irritability, nervousness, malaise, obsessive-compulsive behaviour, paranoia, psychosis, panic attack, tremor, seizures (see also Cautions), neuroleptic malignant syndrome, anhedonia, growth restriction in children (see also Cautions and notes above), hyperpyrexia, renal impairment, sexual dysfunction, acidosis, rhabdomyolysis, mydriasis, visual disturbances, alopecia, rash, sweating, urticaria; central stimulants have provoked choreoathetoid movements and dyskinesia, tics and Tourette syndrome in predisposed individuals (see also Cautions); *very rarely* angle-closure glaucoma; **overdosage:** see Emergency Treatment of Poisoning, p. 30

Indications and dose

Refractory attention deficit hyperactivity disorder initiated by specialist

• By mouth

Child 6–18 years initially 2.5 mg 2–3 times daily, increased if necessary at weekly intervals by 5 mg; usual max. 1 mg/kg daily, up to 20 mg (40 mg daily has been given in some children); maintenance dose given in 2–4 divided doses

Administration tablets can be halved

Dexamfetamine (Non-proprietary) (CD2)

Tablets, scored, dexamfetamine sulfate 5 mg, net price 28-tab pack = £18.90. Counselling, driving

LISDEXAMFETAMINE MESILATE

Note Lisdexamfetamine is a prodrug of dexamfetamine

Cautions see notes above; also anorexia; history of cardiovascular disease or abnormalities; psychosis or bipolar disorder; monitor for aggressive behaviour or

hostility during initial treatment; history of drug or alcohol abuse; may lower seizure threshold (discontinue if seizures occur); tics and Tourette syndrome (use with caution)—discontinue if tics occur; monitor growth in children (see also below); susceptibility to angle-closure glaucoma; avoid abrupt withdrawal; acute porphyria (section 9.8.2); **interactions:**

Appendix 1 (sympathomimetics)

Growth restriction Monitor height and weight as growth restriction may occur during prolonged therapy (drug-free periods may allow catch-up in growth but withdraw slowly to avoid inducing depression or renewed hyperactivity)

Contra-indications symptomatic cardiovascular disease including moderate to severe hypertension and advanced arteriosclerosis, hyperexcitability or agitated states, hyperthyroidism

Renal impairment use with caution

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—present in human milk

Side-effects nausea, decreased appetite, vomiting, diarrhoea, dry mouth, abdominal cramps, dyspnoea, sleep disturbances, tics, aggression, headache, dizziness, drowsiness, mydriasis, labile mood, weight loss, pyrexia, malaise, growth restriction in children (see also under Cautions and notes above); *less commonly* anorexia, tachycardia, palpitation, hypertension, logorrhoea, anxiety, paranoia, restlessness, depression, dysphoria, dermatillomania, mania, hallucination, sweating, tremor, visual disturbances, sexual dysfunction, rash; *very rarely* angle-closure glaucoma; *also reported* cardiomyopathy, euphoria, seizures (see also Cautions); central stimulants have provoked choreoathetoid movements and dyskinesia, and Tourette syndrome in predisposed individuals (see also Cautions); **overdosage:** see Emergency Treatment of Poisoning, p. 30

Indications and dose

Attention deficit hyperactivity disorder (refractory to methylphenidate treatment) initiated by specialist

• By mouth

Child 6–18 years initially 30 mg once daily in the morning, increased if necessary at weekly intervals by 20 mg; max. 70 mg daily (discontinue if response insufficient after 1 month)

Administration Swallow whole or dissolve contents of capsule in a glass of water

Elvanse® (Shire) ▼ [CD2]

Capsule, lisdexamfetamine mesilate 30 mg (white/pink), net price 28-cap pack = £58.24; 50 mg (white/blue), 28-cap pack = £68.60; 70 mg (blue/pink), 28-cap pack = £83.16. Label: 3, 25, counselling, administration

Counselling Swallow whole or dissolve contents of capsule in a glass of water

METHYLPHENIDATE HYDROCHLORIDE

Cautions see notes above; also monitor for psychiatric disorders; anxiety or agitation; tics or a family history of Tourette syndrome; drug or alcohol dependence; epilepsy (discontinue if increased seizure frequency); susceptibility to angle-closure glaucoma; avoid abrupt withdrawal; **interactions:** Appendix 1 (sympathomimetics)

Contra-indications severe depression, suicidal ideation; anorexia nervosa; psychosis; uncontrolled bipolar disorder; hyperthyroidism; cardiovascular disease (including heart failure, cardiomyopathy, severe hypertension, and arrhythmias), structural cardiac abnormalities; phaeochromocytoma; vasculitis; cerebrovascular disorders

Pregnancy limited experience—avoid unless potential benefit outweighs risk

Breast-feeding limited information available—avoid

Side-effects abdominal pain, nausea, vomiting, diarrhoea, dyspepsia, dry mouth, anorexia, reduced weight gain; tachycardia, palpitation, arrhythmias, changes in blood pressure; cough, nasopharyngitis; tics (*very rarely* Tourette syndrome), insomnia, nervousness, asthenia, depression, irritability, aggression, headache, drowsiness, dizziness, movement disorders; fever, arthralgia; rash, pruritus, alopecia; growth restriction; *less commonly* constipation, dyspnoea, abnormal dreams, confusion, suicidal ideation, urinary frequency, haematuria, muscle cramps, edema; *rarely* angina, sweating, visual disturbances; *very rarely* hepatic dysfunction, myocardial infarction, cerebral arteritis, psychosis, seizures, neuroleptic malignant syndrome, tolerance and dependence, blood disorders including leucopenia and thrombocytopenia, angle-closure glaucoma, exfoliative dermatitis, and erythema multiforme; supraventricular tachycardia, bradycardia, and convulsions *also reported*

Licensed use not licensed for use in children under 6 years; doses over 60 mg daily not licensed; doses of *Concerta® XL* over 54 mg daily not licensed

Indications and dose

Attention deficit hyperactivity disorder initiated by specialist

• By mouth

Child 4–6 years 2.5 mg twice daily increased if necessary at weekly intervals by 2.5 mg daily to max. 1.4 mg/kg daily in 2–3 divided doses; discontinue if no response after 1 month

Child 6–18 years initially 5 mg 1–2 times daily, increased if necessary at weekly intervals by 5–10 mg daily; licensed max. 60 mg daily in 2–3 divided doses but may be increased to 2.1 mg/kg daily in 2–3 divided doses (max. 90 mg daily) under the direction of a specialist; discontinue if no response after 1 month

Evening dose If effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose)

Note Treatment may be started using a modified-release preparation

Administration Contents of *Equasym XL®* capsules, and *Medikinet XL®* capsules, can be sprinkled on a tablespoon of apple sauce, then swallowed immediately without chewing

Methylphenidate Hydrochloride (Non-proprietary) [CD2]

Tablets, methylphenidate hydrochloride 5 mg, net price 30-tab pack = £3.03; 10 mg, 30-tab pack = £5.49; 20 mg, 30-tab pack = £10.92

Brands include *Medikinet®*

Ritalin® (Novartis) [CD2]

Tablets, scored, methylphenidate hydrochloride 10 mg, net price 30-tab pack = £5.57

Modified release

Note Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of methylphenidate, prescribers should specify the brand to be dispensed.

Concerta® XL (Janssen) (CD2)

Tablets, m/r, methylphenidate hydrochloride 18 mg (yellow), net price 30-tab pack = £31.19; 27 mg (grey), 30-tab pack = £36.81; 36 mg (white), 30-tab pack = £42.45. Label: 25

Counselling Tablet membrane may pass through gastro-intestinal tract unchanged

Cautions dose form not appropriate for use in dysphagia or if gastro-intestinal lumen restricted

Dose

Attention deficit hyperactivity disorder

• By mouth

Child 6–18 years initially 18 mg once daily (in the morning), increased if necessary at weekly intervals by 18 mg according to response; licensed max. 54 mg once daily, but may be increased to 2.1 mg/kg daily (max. 108 mg daily) under the direction of a specialist; discontinue if no response after 1 month

Note Total daily dose of 15 mg of standard-release formulation is considered equivalent to Concerta® XL 18 mg once daily

Note Concerta® XL tablets consist of an immediate-release component (22% of the dose) and a modified-release component (78% of the dose)

Equasym XL® (Shire) (CD2)

Capsules, m/r, methylphenidate hydrochloride 10 mg (white/green), net price 30-cap pack = £25.00; 20 mg (white/blue), 30-cap pack = £30.00; 30 mg (white/brown), 30-cap pack = £35.00. Label: 25

Dose

Attention deficit hyperactivity disorder

• By mouth

Child 6–18 years initially 10 mg once daily in the morning before breakfast, increased gradually at weekly intervals if necessary; licensed max. 60 mg daily, but may be increased to 2.1 mg/kg daily (max. 90 mg daily) under the direction of a specialist; discontinue if no response after 1 month

Note Contents of capsule can be sprinkled on a tablespoon of apple sauce (then swallowed immediately without chewing)

Note Equasym XL® capsules consist of an immediate-release component (30% of the dose) and a modified-release component (70% of the dose)

Medikinet XL® (Flynn) (CD2)

Capsules, m/r, methylphenidate hydrochloride 5 mg (white), net price 30-cap pack = £24.04; 10 mg (lilac/white), 30-cap pack = £24.04; 20 mg (lilac), 30-cap pack = £28.86; 30 mg (purple/light grey), 30-cap pack = £33.66; 40 mg (purple/grey), 30-cap pack = £57.72. Label: 25

Dose

Attention deficit hyperactivity disorder

• By mouth

Child 6–18 years 10 mg once daily in the morning with breakfast, adjusted at weekly intervals according to response; licensed max. 60 mg daily, but may be increased to 2.1 mg/kg daily (max. 90 mg daily) under the direction of a specialist; discontinue if no response after 1 month

Note Contents of capsule can be sprinkled on a tablespoon of apple sauce, or yoghurt (then swallowed immediately without chewing)

Note Medikinet XL® capsules consist of an immediate-release component (50% of the dose) and a modified-release component (50% of the dose)

4.5 Drugs used in the treatment of obesity

Obesity is associated with many health problems including cardiovascular disease, diabetes mellitus, gallstones, and osteoarthritis. Factors that aggravate obesity may include depression, other psychosocial problems, and some drugs.

The main treatment of the obese individual is a suitable diet, carefully explained to the individual or carer, with appropriate support and encouragement; increased physical activity should also be encouraged. If appropriate, smoking cessation (while maintaining body weight) may be worthwhile before attempting supervised weight loss, since cigarette smoking may be more harmful than obesity.

Obesity should be managed in an appropriate setting by staff who have been trained in the management of obesity in children; the individual or carer should receive advice on diet and lifestyle modification and should be monitored for changes in weight as well as in blood pressure, blood lipids, and other associated conditions.

NICE has recommended (December 2006) that drug treatment should only be considered for obese children after dietary, exercise, and behavioural approaches have been started, and who have associated conditions such as orthopaedic problems or sleep apnoea; treatment is intended both to facilitate weight loss and to maintain reduced weight. Initial treatment should involve a 6–12 month trial of orlistat, with regular reviews of effectiveness, tolerance, and adherence.

Choice Orlistat, a lipase inhibitor, reduces the absorption of dietary fat. Some weight loss in those taking orlistat probably results from a reduction in fat intake to avoid severe gastro-intestinal effects including steatorrhoea. Vitamin supplementation (especially of vitamin D) should be considered.

Thyroid hormones have no place in the treatment of obesity except in biochemically proven hypothyroid children. The use of diuretics, chorionic gonadotrophin, or amfetamines is not appropriate for weight reduction.

ORLISTAT

Cautions may impair absorption of fat-soluble vitamins; chronic kidney disease or volume depletion; **interactions:** Appendix 1 (orlistat)

Multivitamins If a multivitamin supplement is required, it should be taken at least 2 hours after orlistat dose or at bedtime

Contra-indications chronic malabsorption syndrome; cholestasis

Pregnancy use with caution

Breast-feeding avoid—no information available

Side-effects oily leakage from rectum, flatulence, faecal urgency, liquid or oily stools, faecal incontinence, abdominal distension and pain (gastro-intestinal effects minimised by reduced fat intake), tooth and gingival disorders, respiratory infections, malaise, anxiety, headache, menstrual disturbances, urinary-tract infection, hypoglycaemia; *also reported* rectal bleeding, diverticulitis, cholelithiasis, hepatitis, hypothyroidism, oxalate nephropathy, bullous eruptions

Licensed use not licensed for use in children

Indications and dose**Adjunct in obesity** initiated by specialist

• By mouth

Child 12–18 years 120 mg taken immediately before, during, or up to 1 hour after each main meal (max. 120 mg 3 times daily); continue treatment beyond 12 weeks only under specialist recommendation

Note If a meal is missed or contains no fat, the dose of orlistat should be omitted

Xenical® (Roche) **PoM**

Capsules, turquoise, orlistat 120 mg, net price 84-cap pack = £31.63

4.6 Drugs used in nausea and vertigo

Antiemetics should be prescribed only when the cause of vomiting is known because otherwise they may delay diagnosis. Antiemetics are unnecessary and sometimes harmful when the cause can be treated, such as in diabetic ketoacidosis, or in digoxin or antiepileptic overdose.

If antiemetic drug treatment is indicated, the drug is chosen according to the aetiology of vomiting.

Antihistamines are effective against nausea and vomiting resulting from many underlying conditions. There is no evidence that any one antihistamine is superior to another but their duration of action and incidence of adverse effects (drowsiness and antimuscarinic effects) differ.

The **phenothiazines** are dopamine antagonists and act centrally by blocking the chemoreceptor trigger zone. They may be considered for the prophylaxis and treatment of nausea and vomiting associated with diffuse neoplastic disease, radiation sickness, and the emesis caused by drugs such as opioids, general anaesthetics, and cytotoxics. **Prochlorperazine**, **perphenazine**, and **trifluoperazine** are less sedating than **chlorpromazine**; severe dystonic reactions sometimes occur with phenothiazines (see below). Some phenothiazines are available as rectal suppositories, which can be useful in children with persistent vomiting or with severe nausea; for children over 12 years prochlorperazine can also be administered as a buccal tablet which is placed between the upper lip and the gum.

Droperidol is a butyrophenone, structurally related to haloperidol, which blocks dopamine receptors in the chemoreceptor trigger zone.

Other antipsychotic drugs including **haloperidol** and **levomepromazine** (section 4.2.1) are also used for the relief of nausea in palliative care (see Symptom Control, (p. 18) and Continuous Subcutaneous Infusions, (p. 19)).

Metoclopramide is an effective antiemetic and its activity closely resembles that of the phenothiazines. Metoclopramide also acts directly on the gastro-intestinal tract and it may be superior to the phenothiazines for emesis associated with gastroduodenal, hepatic, and biliary disease. Due to the risk of neurological side effects, metoclopramide should only be used in children as second line therapy in postoperative and cytotoxic-induced nausea and vomiting, see also section 8.1, and MHRA advice below.

MHRA/CHM advice**Metoclopramide: risk of neurological adverse effects—restricted dose and duration of use (August 2013)**

The benefits and risks of metoclopramide have been reviewed by the European Medicines Agency's Committee on Medicinal Products for Human Use, which concluded that the risk of neurological effects such as extrapyramidal disorders and tardive dyskinesia outweigh the benefits in long-term or high-dose treatment. To help minimise the risk of potentially serious neurological adverse effects, the following restrictions to indications, dose and duration of use have been made:

- In children aged 1–18 years, metoclopramide should only be used as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting and for treatment of established postoperative nausea and vomiting;
- Use of metoclopramide is contra-indicated in children aged under 1 year;
- Metoclopramide should only be prescribed for short-term use (up to 5 days);
- Recommended dose is 100–150 micrograms/kg, repeated up to 3 times daily;
- Intravenous doses should be administered as a slow bolus over at least 3 minutes;
- Oral liquid formulations should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy.

Note This advice does not apply to unlicensed uses of metoclopramide (e.g. palliative care, p. 16)

Acute dystonic reactions

Phenothiazines and metoclopramide can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible. With metoclopramide, dystonic effects usually occur shortly after starting treatment and subside within 24 hours of stopping it. An antimuscarinic drug such as procyclidine (section 4.9.2) is used to abort dystonic attacks.

Domperidone acts at the chemoreceptor trigger zone; it has the advantage over metoclopramide and the phenothiazines of being less likely to cause central effects such as sedation and dystonic reactions because it does not readily cross the blood-brain barrier. See also MHRA advice below.

MHRA/CHM advice**Domperidone: risk of cardiac side-effects—restricted indication, new contra-indications, reduced dose and duration of use**

The benefits and risks of domperidone have been reviewed. As domperidone is associated with a small increased risk of serious cardiac side-effects, the following restrictions to indication, dose and duration of treatment have been made, and new contra-indications added:

- Domperidone should only be used for the relief of the symptoms of nausea and vomiting;
- Domperidone should be used at the lowest effective dose for the shortest possible duration (max. treatment duration should not normally exceed 1 week);
- Domperidone is contra-indicated for use in conditions where cardiac conduction is, or could be impaired, or where there is underlying cardiac disease, when administered concomitantly with drugs that prolong the QT interval or potent CYP3A4 inhibitors, and in severe hepatic impairment
- The recommended dose in adolescents over 12 years and over 35 kg is 10 mg up to 3 times daily;
- The recommended dose in children under 35 kg is 250 micrograms/kg up to 3 times daily;
- Oral liquid formulations should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy.

Note This advice does not apply to unlicensed uses of domperidone (e.g. palliative care, p. 16)

Granisetron and **ondansetron** are specific 5HT₃-receptor antagonists which block 5HT₃ receptors in the gastro-intestinal tract and in the CNS. They are of value in the management of nausea and vomiting in children receiving cytotoxics and in postoperative nausea and vomiting.

Nabilone is a synthetic cannabinoid with antiemetic properties. It may be used for nausea and vomiting caused by cytotoxic chemotherapy that is unresponsive to conventional antiemetics. Side-effects such as drowsiness and dizziness occur frequently with standard doses.

Dexamethasone (section 6.3.2) has antiemetic effects. For the role of dexamethasone in cytotoxic-induced nausea and vomiting see section 8.1.

Vomiting during pregnancy Nausea in the first trimester of pregnancy is generally mild and does not require drug therapy. On rare occasions if vomiting is severe, short-term treatment with an antihistamine, such as **promethazine**, may be required. **Prochlorperazine** or **metoclopramide** may be considered as second-line treatments (see also MHRA advice above). If symptoms do not settle in 24 to 48 hours then specialist opinion should be sought. Hyperemesis gravidarum is a more serious condition, which requires intravenous fluid and electrolyte replacement and sometimes nutritional support. Supplementation with thiamine must be considered in order to reduce the risk of Wernicke's encephalopathy.

Postoperative nausea and vomiting The incidence of postoperative nausea and vomiting depends on many factors including the anaesthetic used, and the type and duration of surgery. Other risk factors include female sex, non-smokers, a history of postoperative nausea and vomiting or motion sickness, and intra-operative and postoperative use of opioids. Treatment to prevent postoperative nausea and vomiting should

be based on the assessed risk. Drugs used include 5HT₃-receptor antagonists, **droperidol**, **dexamethasone**, some **phenothiazines** (e.g. **prochlorperazine**), and **anti-histamines** (e.g. **cyclizine**). A combination of two or more antiemetic drugs that have different mechanisms of action is often indicated in those at high risk of postoperative nausea and vomiting or where postoperative vomiting presents a particular danger (e.g. in some types of surgery). When a prophylactic antiemetic drug has failed, postoperative nausea and vomiting should be treated with one or more drugs from a different class.

Opioid-induced nausea and vomiting **Cyclizine**, **ondansetron**, and **prochlorperazine** are used to relieve opioid-induced nausea and vomiting; **ondansetron** has the advantage of not producing sedation.

Motion sickness Antiemetics should be given to prevent motion sickness rather than after nausea or vomiting develop. The most effective drug for the prevention of motion sickness is **hyoscine hydrobromide**. For children over 10 years old, a transdermal hyoscine patch provides prolonged activity but it needs to be applied several hours before travelling. The sedating antihistamines are slightly less effective against motion sickness, but are generally better tolerated than hyoscine. If a sedative effect is desired **promethazine** is useful, but generally a slightly less sedating antihistamine such as **cyclizine** or **cinnarizine** is preferred. Domperidone, 5HT₃-receptor antagonists, and the phenothiazines (except the antihistamine phenothiazine **promethazine**) are **ineffective** in motion sickness.

Other vestibular disorders Management of vestibular diseases is aimed at treating the underlying cause as well as treating symptoms of the balance disturbance and associated nausea and vomiting. **Antihistamines** (such as **cinnarizine**), and **phenothiazines** (such as **prochlorperazine**) are effective for prophylaxis and treatment of nausea and vertigo resulting from vestibular disorders; however, when nausea and vertigo are associated with middle ear surgery, treatment can be difficult.

Cytotoxic chemotherapy For the management of nausea and vomiting induced by cytotoxic chemotherapy, see section 8.1.

Palliative care For the management of nausea and vomiting in palliative care, see Symptom Control, (p. 18) and Continuous Subcutaneous Infusions, (p. 19).

Migraine For the management of nausea and vomiting associated with migraine, see 4.7.4.1, (p. 215).

Antihistamines

CINNARIZINE

Cautions section 3.4.1

Contra-indications section 3.4.1

Hepatic impairment section 3.4.1

Renal impairment use with caution—no information available

Pregnancy section 3.4.1

Breast-feeding section 3.4.1

Side-effects section 3.4.1; also rarely weight gain, sweating, lichen planus, and lupus-like skin reactions

Indications and dose**Relief of symptoms of vestibular disorders**

• By mouth

Child 5–12 years 15 mg 3 times daily**Child 12–18 years** 30 mg 3 times daily**Motion sickness**

• By mouth

Child 5–12 years 15 mg 2 hours before travel then 7.5 mg every 8 hours during journey if necessary**Child 12–18 years** 30 mg 2 hours before travel then 15 mg every 8 hours during journey if necessary**Cinnarizine** (Non-proprietary)**Tablets**, cinnarizine 15 mg, net price 84-tab pack = £3.45. Label: 2**Stugeron®** (Janssen)**Tablets**, scored, cinnarizine 15 mg, net price 15-tab pack = £1.77, 100-tab pack = £4.18. Label: 2**CYCLIZINE****Cautions** section 3.4.1; severe heart failure; may counteract haemodynamic benefits of opioids; **interactions**: Appendix 1 (antihistamines)**Skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced**Contra-indications** section 3.4.1**Hepatic impairment** section 3.4.1**Pregnancy** section 3.4.1**Breast-feeding** no information available**Side-effects** section 3.4.1**Licensed use** tablets not licensed for use in children under 6 years; injection not licensed for use in children**Indications and dose****Nausea and vomiting of known cause; nausea and vomiting associated with vestibular disorders and palliative care**

• By mouth or by intravenous injection over 3–5 minutes

Child 1 month–6 years 0.5–1 mg/kg up to 3 times daily; max. single dose 25 mg**Child 6–12 years** 25 mg up to 3 times daily**Child 12–18 years** 50 mg up to 3 times daily**Note** For motion sickness, take 1–2 hours before departure

• By rectum

Child 2–6 years 12.5 mg up to 3 times daily**Child 6–12 years** 25 mg up to 3 times daily**Child 12–18 years** 50 mg up to 3 times daily

• By continuous intravenous or subcutaneous infusion

Child 1 month–2 years 3 mg/kg over 24 hours**Child 2–5 years** 50 mg over 24 hours**Child 6–12 years** 75 mg over 24 hours**Child 12–18 years** 150 mg over 24 hours**Administration** for administration *by mouth*, tablets may be crushed**Cyclizine** (Non-proprietary)**Tablets**, cyclizine hydrochloride 50 mg, net price 100-tab pack = £10.72. Label: 2**Suppositories**, 12.5 mg, 25 mg, 50 mg, 100 mg. Available from 'special-order' manufacturers or specialist importing companies, see p. 840**Valoid®** (AMCo) (PoM)**Injection**, cyclizine lactate 50 mg/mL, net price 1-mL amp = 65p**PROMETHAZINE HYDROCHLORIDE****Cautions** see notes in section 3.4.1**Contra-indications** see Promethazine Hydrochloride, section 3.4.1**Hepatic impairment** see notes in section 3.4.1**Renal impairment** see Promethazine Hydrochloride, section 3.4.1**Pregnancy** see notes in section 3.4.1**Breast-feeding** see notes in section 3.4.1**Side-effects** see Promethazine Hydrochloride, section 3.4.1 but more sedating**Indications and dose****Nausea and vomiting**

• By mouth

Child 2–5 years 5 mg at bedtime on night before travel, repeat following morning if necessary**Child 5–10 years** 10 mg at bedtime on night before travel, repeat following morning if necessary**Child 10–18 years** 20–25 mg at bedtime on night before travel, repeat following morning if necessary**Allergy and urticaria** section 3.4.1**Sedation** section 4.1.1**Preparations**

Section 3.4.1

PROMETHAZINE TEOCLATE**Cautions** section 3.4.1; severe coronary artery disease; asthma, bronchitis, bronchiectasis, Reye's syndrome**Contra-indications** section 3.4.1**Hepatic impairment** section 3.4.1**Renal impairment** use with caution**Pregnancy** section 3.4.1**Breast-feeding** section 3.4.1**Side-effects** section 3.4.1**Licensed use** not licensed to treat vomiting of pregnancy**Indications and dose****Nausea, vomiting, labyrinthine disorders**

• By mouth

Child 5–10 years 12.5–37.5 mg daily**Child 10–18 years** 25–75 mg daily (max. 100 mg)**Motion sickness prevention**

• By mouth

Child 5–10 years 12.5 mg at bedtime on night before travel or 12.5 mg 1–2 hours before travel

Child 10–18 years 25 mg at bedtime on night before travel *or* 25 mg 1–2 hours before travel

Motion sickness treatment

- By mouth

Child 5–10 years 12.5 mg at onset, then 12.5 mg at bedtime for 2 days

Child 10–18 years 25 mg at onset, then 25 mg at bedtime for 2 days

Severe vomiting during pregnancy

- By mouth

25 mg at bedtime increased if necessary to max. 100 mg daily (but see also Vomiting During Pregnancy, p. 193)

Avomine® (Manx)

Tablets, scored, promethazine teoclate 25 mg, net price 10-tab pack = £1.13; 28-tab pack = £3.13. Label: 2

Phenothiazines and related drugs

CHLORPROMAZINE HYDROCHLORIDE

Cautions see Chlorpromazine Hydrochloride, section 4.2.1

Contra-indications see notes in section 4.2.1

Hepatic impairment see notes in section 4.2.1

Renal impairment see notes in section 4.2.1

Pregnancy see notes in section 4.2.1

Breast-feeding see notes in section 4.2.1

Side-effects see Chlorpromazine Hydrochloride, section 4.2.1

Indications and dose

Nausea and vomiting of terminal illness (where other drugs are unsuitable)

- By mouth

Child 1–6 years 500 micrograms/kg every 4–6 hours; max. 40 mg daily

Child 6–12 years 500 micrograms/kg every 4–6 hours; max. 75 mg daily

Child 12–18 years 10–25 mg every 4–6 hours

- By deep intramuscular injection

Child 1–6 years 500 micrograms/kg every 6–8 hours; max. 40 mg daily

Child 6–12 years 500 micrograms/kg every 6–8 hours; max. 75 mg daily

Child 12–18 years initially 25 mg then 25–50 mg every 3–4 hours until vomiting stops

Preparations

Section 4.2.1

DROPERIDOL

Cautions section 4.2.1; also chronic obstructive pulmonary disease or respiratory failure; electrolyte disturbances; history of alcohol abuse; continuous pulse oximetry required if risk of ventricular arrhythmia—continue for 30 minutes following administration; interactions: Appendix 1 (droperidol)

Contra-indications section 4.2.1; QT-interval prolongation (avoid concomitant administration of drugs

that prolong QT interval); hypokalaemia; hypomagnesaemia; bradycardia

Hepatic impairment max. 625 micrograms repeated every 6 hours as required

Renal impairment max. 625 micrograms repeated every 6 hours as required

Pregnancy section 4.2.1

Breast-feeding limited information available—avoid repeated administration

Side-effects section 4.2.1; also anxiety, cardiac arrest, hallucinations, and inappropriate secretion of anti-diuretic hormone

Indications and dose

Prevention and treatment of postoperative nausea and vomiting

- By intravenous injection

Child 2–18 years 20–50 micrograms/kg (max. 1.25 mg) 30 minutes before the end of surgery, repeated every 6 hours as necessary

Xomolix® (ProStrakan) (PoM)

Injection, droperidol 2.5 mg/mL, net price 1-mL amp = £3.94

PERPHENAZINE

Cautions see notes in section 4.2.1

Contra-indications see notes in section 4.2.1

Hepatic impairment see notes in section 4.2.1

Renal impairment see notes in section 4.2.1

Pregnancy see notes in section 4.2.1

Breast-feeding see notes in section 4.2.1

Side-effects see Perphenazine, section 4.2.1

Indications and dose

Severe nausea and vomiting unresponsive to other antiemetics

- By mouth

Child 14–18 years 4 mg 3 times daily, adjusted according to response, max. 24 mg daily

Preparations

Section 4.2.1

PROCHLORPERAZINE

Cautions see notes in section 4.2.1; hypotension more likely after intramuscular injection

Contra-indications see notes in section 4.2.1

Hepatic impairment see notes in section 4.2.1

Renal impairment see notes in section 4.2.1

Pregnancy see notes in section 4.2.1

Breast-feeding see notes in section 4.2.1

Side-effects see notes in section 4.2.1; respiratory depression may occur in susceptible children

Licensed use injection not licensed for use in children

Indications and dose

Prevention and treatment of nausea and vomiting

- By mouth

Child 1–12 years and over 10 kg 250 micrograms/kg 2–3 times daily

Child 12–18 years 5–10 mg, repeated if necessary up to 3 times daily

- By intramuscular injection

Child 2–5 years, 1.25–2.5 mg, repeated if necessary up to 3 times daily

Child 5–12 years 5–6.25 mg, repeated if necessary up to 3 times daily

Child 12–18 years 12.5 mg, repeated if necessary up to 3 times daily

Note Doses are expressed as prochlorperazine maleate or mesilate; 1 mg prochlorperazine maleate = 1 mg prochlorperazine mesilate

Prochlorperazine (Non-proprietary) (PoM)

Tablets, prochlorperazine maleate 5 mg, net price 28-tab pack = 95p, 84-tab pack = £1.37. Label: 2

Injection, prochlorperazine mesilate 12.5 mg/mL, net price 1-mL amp = 52p

Stemetil® (Sanofi-Aventis) (PoM)

Tablets, prochlorperazine maleate 5 mg (off-white), net price 28-tab pack = £1.98, 84-tab pack = £5.94. Label: 2

Syrup, straw-coloured, prochlorperazine mesilate 5 mg/5 mL, net price 100-mL pack = £3.34. Label: 2

Injection, prochlorperazine mesilate 12.5 mg/mL, net price 1-mL amp = 52p

Buccal preparation

Buccastem® (Alliance) (PoM)

Tablets (buccal), pale yellow, prochlorperazine maleate 3 mg, net price 5 × 10-tab pack = £6.49. Label: 2, counselling, administration, see under Dose below

Dose

- By mouth

Child 12–18 years 1–2 tablets twice daily; tablets are placed high between upper lip and gum and left to dissolve

TRIFLUOPERAZINE

Cautions see notes in section 4.2.1

Contra-indications see notes in section 4.2.1

Hepatic impairment see notes in section 4.2.1

Renal impairment see notes in section 4.2.1

Pregnancy see notes in section 4.2.1

Breast-feeding see notes in section 4.2.1

Side-effects see Trifluoperazine section 4.2.1

Indications and dose

Severe nausea and vomiting unresponsive to other antiemetics

- By mouth

Child 3–5 years up to 500 micrograms twice daily

Child 6–12 years up to 2 mg twice daily

Child 12–18 years 1–2 mg twice daily; max. 3 mg twice daily

Preparations

Section 4.2.1

Domperidone and metoclopramide

DOMPERIDONE

Cautions children; interactions: Appendix 1 (domperidone)

Counselling Children and their carers should be told how to recognise signs of arrhythmia and advised to seek medical

attention if symptoms such as palpitation or syncope develop

Contra-indications prolactinaemia; if increased gastro-intestinal motility harmful; conditions where cardiac conduction is, or could be, impaired; concomitant use of drugs that prolong the QT interval, or of potent CYP3A4 inhibitors; cardiac disease

Hepatic impairment avoid in moderate or severe impairment

Renal impairment reduce frequency

Pregnancy use only if potential benefit outweighs risk

Breast-feeding amount too small to be harmful

Side-effects dry mouth; *less commonly* diarrhoea, drowsiness, malaise, headache, anxiety, decreased libido, galactorrhoea, breast pain, rash, pruritus; *also reported* QT-interval prolongation, ventricular arrhythmias, sudden cardiac death, agitation, nervousness, convulsions, extrapyramidal disorders, gynaecomastia, amenorrhoea, urinary retention, oculogyric crisis

Indications and dose

Symptomatic relief of nausea and vomiting

- By mouth

Child over 1 month and body-weight up to 35 kg 250 micrograms/kg up to 3 times daily; max. 750 micrograms/kg in 24 hours

Child over 12 years and body-weight 35 kg and over 10 mg up to 3 times daily, max. 30 mg daily

Note See also MHRA advice above

Domperidone (Non-proprietary) (PoM)

Tablets, 10 mg (as maleate), net price 30-tab pack = £1.39; 100-tab pack = £4.63. Label: 22, counselling, arrhythmias

Suspension, domperidone 5 mg/5 mL, net price 200-mL pack = £12.53. Label: 22, counselling, arrhythmias

Motilium® (Zentiva) (PoM)

Tablets, f/c, domperidone 10 mg (as maleate), net price 30-tab pack = £2.71; 100-tab pack = £9.04. Label: 22, counselling, arrhythmias

METOCLOPRAMIDE HYDROCHLORIDE

Cautions atopic allergy (including asthma); cardiac conduction disturbances (and concomitant use of other drugs affecting cardiac conduction); uncorrected electrolyte imbalance; bradycardia; may mask underlying disorders such as cerebral irritation; epilepsy; interactions: Appendix 1 (metoclopramide)

Contra-indications gastro-intestinal obstruction, perforation or haemorrhage; 3–4 days after gastro-intestinal surgery; pheochromocytoma

Hepatic impairment reduce dose

Renal impairment avoid or use small dose in severe impairment; increased risk of extrapyramidal reactions

Pregnancy not known to be harmful

Breast-feeding small amount present in milk; avoid

Side-effects extrapyramidal effects (see p. 192), hyperprolactinaemia, galactorrhoea, gynaecomastia, menstrual changes; *very rarely* cardiac conduction abnormalities reported following intravenous administration, depression, neuroleptic malignant syndrome, methaemoglobinemia (more severe in G6PD deficiency); *also reported* diarrhoea, hypo-

tension, dyspnoea, anxiety, confusion, restlessness, drowsiness, dizziness, tremor, tardive dyskinesia on prolonged administration, visual disturbances, rash, urticaria, pruritus, oedema

Licensed use *Maxolon*® tablets not licensed for use in children

Indications and dose

Second-line option for treatment of established postoperative nausea and vomiting and prevention of delayed chemotherapy-induced nausea and vomiting

- By mouth, or by intramuscular injection, or by intravenous injection over at least 3 minutes

Child 1–18 years 100–150 micrograms/kg up to 3 times daily

Note See MHRA advice above

Administration Oral liquid preparation to be given via a graduated oral dosing syringe

Metoclopramide (Non-proprietary) (PoM)

Tablets, metoclopramide hydrochloride 10 mg, net price 28-tab pack = 87p

Oral solution, metoclopramide hydrochloride 5 mg/5 mL, net price 150-mL pack = £17.14. Counselling, use of pipette

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Injection, metoclopramide hydrochloride 5 mg/mL, net price 2-mL amp = 30p

Maxolon® (AMCo) (PoM)

Tablets, scored, metoclopramide hydrochloride 10 mg, net price 84-tab pack = £5.24

Injection, metoclopramide hydrochloride 5 mg/mL, net price 2-mL amp = 27p

5HT₃-receptor antagonists

GRANISETRON

Cautions susceptibility to QT-interval prolongation (including concomitant use of drugs that prolong QT interval, and electrolyte disturbances); subacute intestinal obstruction

Hepatic impairment manufacturer advises use with caution

Pregnancy manufacturer advises avoid

Breast-feeding avoid—no information available

Side-effects constipation, diarrhoea, headache, insomnia; *less commonly* QT-interval prolongation, extrapyramidal reactions, rash

Licensed use tablets not licensed in children (age range not specified by manufacturer)

Indications and dose

Treatment and prevention of nausea and vomiting induced by chemotherapy

- By mouth

Child 12–18 years 1–2 mg within 1 hour before start of treatment, then 2 mg daily in 1–2 divided doses for up to 1 week following chemotherapy

- By intravenous infusion

Child 2–18 years prevention, 10–40 micrograms/kg (max. 3 mg) before start of chemotherapy; treatment, dose as for prevention repeated within 24 hours if necessary (not less than 10 minutes after initial dose); total max. 2 doses in 24 hours

Administration for *intravenous infusion*, dilute up to 3 mL of granisetron injection in Glucose 5% or Sodium Chloride 0.9% to a total volume of 10–30 mL; give over 5 minutes

Granisetron (Non-proprietary) (PoM)

Tablets, granisetron (as hydrochloride) 1 mg, net price 10-tab pack = £50.38

Injection, granisetron (as hydrochloride) 1 mg/mL, for dilution before use, net price 1-mL amp = £1.60, 3-mL amp = £2.40

Kytril® (Roche) (PoM)

Tablets, f/c, granisetron (as hydrochloride) 1 mg, net price 10-tab pack = £52.39; 2 mg, 5-tab pack = £52.39

ONDANSETRON

Cautions susceptibility to QT-interval prolongation (including concomitant use of drugs that prolong QT interval, and electrolyte disturbances); subacute intestinal obstruction; adenotonsillar surgery

Contra-indications congenital long QT syndrome

Hepatic impairment reduce dose in moderate or severe impairment

Pregnancy no information available; avoid unless potential benefit outweighs risk

Breast-feeding present in milk in *animal studies*—avoid

Side-effects constipation; headache; flushing; injection-site reactions; *less commonly* hiccups, hypotension, bradycardia, chest pain, arrhythmias, movement disorders, seizures; *on intravenous administration*, rarely dizziness, transient visual disturbances (*very rarely* transient blindness)

Licensed use not licensed for radiotherapy-induced nausea and vomiting in children

Indications and dose

Prevention and treatment of chemotherapy- and radiotherapy-induced nausea and vomiting

- By intravenous infusion over at least 15 minutes

Child 6 months–18 years either 5 mg/m² immediately before chemotherapy (8 mg if body surface area greater than 1.2 m²), then give by mouth, or 150 micrograms/kg immediately before chemotherapy (max. single dose 8 mg) repeated every 4 hours for 2 further doses, then give by mouth; max. total daily dose 32 mg

- By mouth following intravenous administration

Note Oral dosing can start 12 hours after intravenous administration

Child 6 months–18 years

Body surface area less than 0.6 m² or body-weight 10 kg or less 2 mg every 12 hours for up to 5 days (max. total daily dose 32 mg)

Body surface area 0.6 m²–1.2 m² or body-weight over 10 kg 4 mg every 12 hours for up to 5 days (max. total daily dose 32 mg)

Body surface area greater than 1.2 m² or body-weight over 40 kg 8 mg every 12 hours for up to 5 days (max. total daily dose 32 mg)

Treatment and prevention of postoperative nausea and vomiting

- By slow intravenous injection over at least 30 seconds

Child 1 month–18 years 100 micrograms/kg (max. 4 mg) as a single dose before, during, or after induction of anaesthesia

Administration for intravenous infusion, dilute to a concentration of 320–640 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; give over at least 15 minutes

Ondansetron (Non-proprietary) (PoM)

Tablets, ondansetron (as hydrochloride) 4 mg, net price 30-tab pack = £5.37; 8 mg, 10-tab pack = £39.80

Brands include Ondemet®

Oral solution, ondansetron (as hydrochloride) 4 mg/5 mL, net price 50-mL pack = £35.76

Brands include Demorem®

Orodispersible film, ondansetron 4 mg, net price 10-film pack = £28.50; 8 mg, 10-film pack = £57.00.

Counselling, administration

Counselling Films should be placed on the tongue, allowed to disperse and swallowed

Brands include Setofil®

Injection, ondansetron (as hydrochloride) 2 mg/mL, net price 2-mL amp = £1.00, 4-mL amp = £11.39

Brands include Ondemet®

Zofran® (GSK) (PoM)

Tablets, yellow, f/c, ondansetron (as hydrochloride) 4 mg, net price 30-tab pack = £107.91; 8 mg, 10-tab pack = £71.94

Oral lyophilisates (Zofran Melt®), ondansetron 4 mg, net price 10-tab pack = £35.97; 8 mg, 10-tab pack = £71.94.

Counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling Tablets should be placed on the tongue, allowed to disperse and swallowed

Oral solution, sugar-free, strawberry-flavoured, ondansetron (as hydrochloride) 4 mg/5 mL, net price 50-mL pack = £35.97

Injection, ondansetron (as hydrochloride) 2 mg/mL, net price 2-mL amp = £5.99; 4-mL amp = £11.99

Cannabinoid**NABILONE**

Cautions history of psychiatric disorder; hypertension; heart disease; adverse effects on mental state can persist for 48–72 hours after stopping

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Hepatic impairment avoid in severe impairment

Pregnancy avoid unless essential

Breast-feeding avoid—no information available

Side-effects drowsiness, vertigo, euphoria, dry mouth, ataxia, visual disturbance, concentration difficulties, sleep disturbance, dysphoria, hypotension, headache and nausea; also confusion, disorientation, hallucinations, psychosis, depression, decreased coordination, tremors, tachycardia, decreased appetite, and abdominal pain

Behavioural effects Children and carers should be made aware of possible changes of mood and other adverse behavioural effects

Licensed use not licensed for use in children

Indications and dose

Nausea and vomiting caused by cytotoxic chemotherapy, unresponsive to conventional antiemetics (under close observation, preferably in hospital setting)

- By mouth

Consult local treatment protocol for details

Nabilone (Meda) (CD2)

Capsules, blue/white, nabilone 1 mg, net price 20-cap pack = £125.84. Label: 2, counselling, behavioural effects

Hyoscine**HYOSCINE HYDROBROMIDE**
(Scopolamine Hydrobromide)

Cautions section 1.2; also epilepsy

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving) and may persist for up to 24 hours or longer after removal of patch; effects of alcohol enhanced

Contra-indications section 1.2

Hepatic impairment use with caution

Renal impairment use with caution

Pregnancy use only if potential benefit outweighs risk; injection may depress neonatal respiration

Breast-feeding amount too small to be harmful

Side-effects section 1.2

Licensed use not licensed for use in excessive respiratory secretions or hypersalivation associated with clozapine therapy

Indications and dose**Motion sickness**

- By mouth

Child 4–10 years 75–150 micrograms 30 minutes before start of journey, repeated every 6 hours if required; max. 3 doses in 24 hours

Child 10–18 years 150–300 micrograms 30 minutes before start of journey, repeated every 6 hours if required; max. 3 doses in 24 hours

- By topical application

Child 10–18 years apply 1 patch (1 mg) to hairless area of skin behind ear 5–6 hours before journey; replace if necessary after 72 hours, siting replacement patch behind the other ear

Excessive respiratory secretions

- By mouth or by sublingual administration

Child 2–12 years 10 micrograms/kg, max. 300 micrograms 4 times daily

Child 12–18 years 300 micrograms 4 times daily

- By transdermal route

Child 1 month–3 years 250 micrograms every 72 hours (quarter of a patch)

Child 3–10 years 500 micrograms every 72 hours (half a patch)

Child 10–18 years 1 mg every 72 hours (one patch)

- By subcutaneous injection, intravenous injection, intravenous infusion, or subcutaneous infusion
See Continuous Subcutaneous Infusions, (p. 19) and Excessive Respiratory Secretions in Palliative Care, (p. 18).

Hypersalivation associated with clozapine therapy

• By mouth

Child 12–18 years 300 micrograms up to 3 times daily; max. 900 micrograms daily

Premedication section 15.1.3

Administration patch applied to hairless area of skin behind ear; if less than whole patch required **either** cut with scissors along full thickness ensuring membrane is not peeled away **or** cover portion to prevent contact with skin

For administration *by mouth*, injection solution may be given orally

Joy-Rides® (Forest)

Tablets, chewable, hyoscine hydrobromide 150 micrograms, net price 12-tab pack = £1.55. Label: 2, 24

Kwells® (Bayer Consumer Care)

Tablets, chewable, hyoscine hydrobromide 150 micrograms (*Kwells® Kids*), net price 12-tab pack = £1.67; 300 micrograms, 12-tab pack = £1.67. Label: 2

Scopoderm TTS® (Novartis Consumer Health) (PoM)

Patch, self-adhesive, pink, releasing hyoscine approx. 1 mg/72 hours when in contact with skin, net price 5 = £8.64. Label: 19, counselling, see below

Counselling Explain accompanying instructions to child and carer, in particular emphasise advice to wash hands after handling and to wash application site after removing, and to use one patch at a time

4.7 Analgesics

4.7.1 Non-opioid analgesics and compound analgesic preparations**4.7.2 Opioid analgesics****4.7.3 Neuropathic pain****4.7.4 Antimigraine drugs**

The non-opioid drugs (section 4.7.1), paracetamol and ibuprofen (and other NSAIDs), are particularly suitable for pain in musculoskeletal conditions, whereas the opioid analgesics (section 4.7.2) are more suitable for moderate to severe pain, particularly of visceral origin.

Pain in palliative care For advice on pain relief in palliative care, see Pain Management With Opioids, (p. 16).

Pain in sickle-cell disease The pain of mild sickle-cell crises is managed with paracetamol, an NSAID (section 10.1.1), codeine, or dihydrocodeine. Severe crises may require the use of morphine or diamorphine; concomitant use of an NSAID may potentiate analgesia and allow lower doses of the opioid to be used. A mixture of nitrous oxide and oxygen (*Entonox®*, *Equanox®*) may also be used.

Dental and orofacial pain Analgesics should be used judiciously in dental care as a **temporary** measure until the cause of the pain has been dealt with.

Dental pain of inflammatory origin, such as that associated with pulpitis, apical infection, localised osteitis or pericoronitis is usually best managed by treating the infection, providing drainage, restorative procedures,

and other local measures. Analgesics provide temporary relief of pain (usually for about 1 to 7 days) until the causative factors have been brought under control. In the case of pulpitis, intra-osseous infection or abscess, reliance on analgesics alone is usually inappropriate.

Similarly the pain and discomfort associated with acute problems of the oral mucosa (e.g. acute herpetic gingivostomatitis, erythema multiforme) may be relieved by **benzydamine** (p. 550) or topical anaesthetics until the cause of the mucosal disorder has been dealt with. However, where a child is febrile, the antipyretic action of **paracetamol** (p. 200) or **ibuprofen** (p. 508) is often helpful.

The *choice* of an analgesic for dental purposes should be based on its suitability for the child. Most dental pain is relieved effectively by non-steroidal anti-inflammatory drugs (NSAIDs) e.g. **ibuprofen** (section 10.1.1). **Paracetamol** has analgesic and antipyretic effects but no anti-inflammatory effect.

Opioid analgesics (section 4.7.2) such as **dihydrocodeine** act on the central nervous system and are traditionally used for *moderate to severe pain*. However, opioid analgesics are relatively ineffective in dental pain and their side-effects can be unpleasant.

Combining a non-opioid with an opioid analgesic can provide greater relief of pain than either analgesic given alone. However, this applies only when an adequate dose of each analgesic is used. Most combination analgesic preparations have not been shown to provide greater relief of pain than an adequate dose of the non-opioid component given alone. Moreover, combination preparations have the disadvantage of an increased number of side-effects.

Any analgesic given before a dental procedure should have a low risk of increasing postoperative bleeding. In the case of pain after the dental procedure, taking an analgesic before the effect of the local anaesthetic has worn off can improve control. Postoperative analgesia with ibuprofen is usually continued for about 24 to 72 hours.

Dysmenorrhoea Paracetamol or a NSAID (section 10.1.1) will generally provide adequate relief of pain from dysmenorrhoea. Alternatively use of a combined hormonal contraceptive in adolescent girls may prevent the pain.

4.7.1 Non-opioid analgesics and compound analgesic preparations

Paracetamol has analgesic and antipyretic properties but no demonstrable anti-inflammatory activity; unlike opioid analgesics, it does not cause respiratory depression and is less irritant to the stomach than the NSAIDs. **Overdosage** with paracetamol is particularly dangerous as it may cause hepatic damage which is sometimes not apparent for 4 to 6 days (see Emergency Treatment of Poisoning, p. 26).

Non-steroidal anti-inflammatory analgesics (NSAIDs, section 10.1.1) are particularly useful for the treatment of children with chronic disease accompanied by pain and inflammation. Some of them are also used in the short-term treatment of mild to moderate pain including transient musculoskeletal pain but paracetamol is now often preferred. They are also suitable for the

relief of pain in *dysmenorrhoea* and to treat pain caused by *secondary bone tumours*, many of which produce lysis of bone and release prostaglandins (see Pain in Palliative Care, (p. 16)). Due to an association with Reye's syndrome (section 2.9), **aspirin** should be avoided in children under 16 years except in Kawasaki disease or for its antiplatelet action (section 2.9). Several NSAIDs are also used for postoperative analgesia (section 15.1.4.2).

Dental and orofacial pain Most dental pain is relieved effectively by NSAIDs (section 10.1.1).

Paracetamol is less irritant to the stomach than NSAIDs. Paracetamol is a suitable analgesic for children; sugar-free versions can be requested by specifying 'sugar-free' on the prescription.

For further information on the management of dental and orofacial pain, see p. 199.

Compound analgesic preparations

Compound analgesic preparations that contain a simple analgesic (such as paracetamol) with an opioid component reduce the scope for effective titration of the individual components in the management of pain of varying intensity.

Compound analgesic preparations containing paracetamol with a *low dose* of an opioid analgesic (e.g. 8 mg of codeine phosphate per compound tablet) may be used in older children but the advantages have not been substantiated. The low dose of the opioid may be enough to cause opioid side-effects (in particular, constipation) and can complicate the treatment of **overdose** (see p. 27) yet may not provide significant additional relief of pain.

A *full dose* of the opioid component (e.g. 60 mg codeine phosphate) in compound analgesic preparations effectively augments the analgesic activity but is associated with the full range of opioid side-effects (including nausea, vomiting, severe constipation, drowsiness, respiratory depression, and risk of dependence on long-term administration). For details of the **side-effects** of opioid analgesics, see p. 203.

In general, when assessing pain, it is necessary to weigh up carefully whether there is a need for a non-opioid and an opioid analgesic to be taken simultaneously.

PARACETAMOL (Acetaminophen)

Cautions alcohol dependence; hepatocellular insufficiency, chronic alcoholism, chronic malnutrition, or dehydration, max. daily infusion dose 3 g in patients greater than 50 kg body-weight with risk factors for hepatotoxicity; before administering, check when paracetamol last administered and cumulative paracetamol dose over previous 24 hours; **interactions:** Appendix 1 (paracetamol)

Hepatic impairment dose-related toxicity—avoid large doses; see also Cautions

Renal impairment increase infusion dose interval to every 6 hours if estimated glomerular filtration rate less than 30 mL/minute/1.73m²

Pregnancy not known to be harmful

Breast-feeding amount too small to be harmful

Side-effects side-effects *rare* malaise, skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous

pustulosis; blood disorders including thrombocytopenia, leucopenia, neutropenia reported; hypotension, flushing, and tachycardia reported on infusion; **important:** liver damage (and less frequently renal damage) following **overdose**, see Emergency Treatment of Poisoning, p. 26

Licensed use not licensed for use in children under 2 months by mouth; not licensed for use in preterm neonates by intravenous infusion; not licensed for use in children under 3 months by rectum; paracetamol oral suspension 500 mg/5 mL not licensed for use in children under 16 years

Indications and dose

Pain; pyrexia with discomfort

• By mouth

Neonate 28–32 weeks corrected gestational age

20 mg/kg as a single dose then 10–15 mg/kg every 8–12 hours as necessary; max. 30 mg/kg daily in divided doses

Neonate over 32 weeks corrected gestational age

20 mg/kg as a single dose then 10–15 mg/kg every 6–8 hours as necessary; max. 60 mg/kg daily in divided doses

Child 1–3 months 30–60 mg every 8 hours as necessary; max. 60 mg/kg daily in divided doses

Child 3–6 months 60 mg every 4–6 hours (max. 4 doses in 24 hours)

Child 6 months–2 years 120 mg every 4–6 hours (max. 4 doses in 24 hours)

Child 2–4 years 180 mg every 4–6 hours (max. 4 doses in 24 hours)

Child 4–6 years 240 mg every 4–6 hours (max. 4 doses in 24 hours)

Child 6–8 years 240–250 mg every 4–6 hours (max. 4 doses in 24 hours)

Child 8–10 years 360–375 mg every 4–6 hours (max. 4 doses in 24 hours)

Child 10–12 years 480–500 mg every 4–6 hours (max. 4 doses in 24 hours)

Child 12–16 years 480–750 mg every 4–6 hours (max. 4 doses in 24 hours)

Child 16–18 years 500 mg–1 g every 4–6 hours (max. 4 doses in 24 hours)

• By rectum

Neonate 28–32 weeks corrected gestational age

20 mg/kg as a single dose then 10–15 mg/kg every 12 hours as necessary; max. 30 mg/kg daily in divided doses

Neonate over 32 weeks corrected gestational age

30 mg/kg as a single dose then 15–20 mg/kg every 8 hours as necessary; max. 60 mg/kg daily in divided doses

Child 1–3 months 30–60 mg every 8 hours as necessary; max. 60 mg/kg daily in divided doses

Child 3–12 months 60–125 mg every 4–6 hours as necessary (max. 4 doses in 24 hours)

Child 1–5 years 125–250 mg every 4–6 hours as necessary (max. 4 doses in 24 hours)

Child 5–12 years 250–500 mg every 4–6 hours as necessary (max. 4 doses in 24 hours)

Child 12–18 years 500 mg every 4–6 hours

- **By intravenous infusion over 15 minutes**
Preterm neonate over 32 weeks corrected gestational age 7.5 mg/kg every 8 hours; max. 25 mg/kg daily
- **Neonate** 10 mg/kg every 4–6 hours; max. 30 mg/kg daily
- **Child body-weight under 10 kg** 10 mg/kg every 4–6 hours; max. 30 mg/kg daily
- **Child body-weight 10–50 kg** 15 mg/kg every 4–6 hours; max. 60 mg/kg daily
- **Child body-weight over 50 kg** 1 g every 4–6 hours; max. 4 g daily

Administration for intravenous infusion, see under individual preparations

Postoperative pain

- **By mouth**
Child 1 month–6 years 20–30 mg/kg as a single dose then 15–20 mg/kg every 4–6 hours; max. 75 mg/kg daily in divided doses
Child 6–12 years 20–30 mg/kg (max. 1 g) as a single dose then 15–20 mg/kg every 4–6 hours; max. 75 mg/kg (max. 4 g) daily in divided doses
Child 12–18 years 1 g every 4–6 hours (max. 4 doses in 24 hours)
- **By rectum**
Child 1–3 months 30 mg/kg as a single dose then 15–20 mg/kg every 4–6 hours; max. 75 mg/kg daily in divided doses
Child 3 months–6 years 30–40 mg/kg as a single dose then 15–20 mg/kg every 4–6 hours; max. 75 mg/kg daily in divided doses
Child 6–12 years 30–40 mg/kg (max. 1 g) as a single dose then 15–20 mg/kg every 4–6 hours; max. 75 mg/kg (max. 4 g) daily in divided doses
Child 12–18 years 1 g every 4–6 hours (max. 4 doses in 24 hours)

Post-immunisation pyrexia in infants (see also p. 605)

- **By mouth**
Child 2–3 months 60 mg as a single dose repeated once after 4–6 hours if necessary

Paracetamol (Non-proprietary)

Tablets and caplets ^(PoM) 1, paracetamol 500 mg, net price 32-tab pack = 84p, 100-tab pack = £2.63. Label: 29, 30

Dental prescribing on NHS Paracetamol Tablets may be prescribed

Capsules ^(PoM) 1, paracetamol 500 mg, net price 32-cap pack = £1.15, 100-cap pack = £3.59. Label: 29, 30

Soluble tablets (= Dispersible tablets) ^(PoM), paracetamol 500 mg, net price 24-tab pack = £2.00, 100-tab pack = £8.33 Label: 13, 29, 30

Dental prescribing on NHS Paracetamol Soluble Tablets 500 mg may be prescribed

Oral suspension 120 mg/5 mL, paracetamol 120 mg/5 mL, net price 100 mL = 71p, 500 mL = £3.06. Label: 30

Note BP directs that when Paediatric Paracetamol Oral Suspension or Paediatric Paracetamol Mixture is prescribed Paracetamol Oral Suspension 120 mg/5 mL should be dispensed; sugar-free versions can be ordered by specifying 'sugar-free' on the prescription

Oral suspension 250 mg/5 mL, paracetamol 250 mg/5 mL, net price 100 mL = £1.19, 200 mL = £1.65. Label: 30

Dental prescribing on NHS Paracetamol Oral Suspension may be prescribed

Oral suspension 500 mg/5 mL ^(PoM), paracetamol 500 mg/5 mL sugar-free, net price 150 mL = £20.00. Label: 30

Suppositories, paracetamol 60 mg, net price 10 = £11.95; 120 mg, 10 = £10.78; 125 mg, 10 = £13.80; 240 mg, 10 = £21.07; 250 mg, 10 = £27.60; 500 mg, 10 = £36.32; 1 g, 12 = £60.00. Label: 30

Note Other strengths available from 'special-order' manufacturers or specialist importing companies, see p. 840

Intravenous infusion ^(PoM), paracetamol 10 mg/mL, net price 100-mL vial = £1.20

Administration give undiluted; for children under 33 kg, use 50-mL vial and dilute if necessary, see *Perfalgan*®

Panadol OA® (GSK) ^(PoM)

Tablets, f/c, paracetamol 1 g, net price 100-tab pack = £3.45. Label: 30

Dose

Pain, pyrexia

- **By mouth**

Child 12–18 years 1 tablet up to 4 times daily, not more often than every 4 hours

Perfalgan® (Bristol-Myers Squibb) ^(PoM)

Intravenous infusion, paracetamol 10 mg/mL, net price 50-mL vial = £1.13, 100-mL vial = £1.25

Administration give undiluted or dilute to a concentration of not less than 1 mg/mL in Glucose 5% or Sodium Chloride 0.9%; use within 1 hour of dilution

With codeine phosphate 8 mg

When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and **no strength is stated**, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate 8 mg and paracetamol 500 mg should be dispensed.

See warnings and notes p. 200

For prescribing information on codeine, see p. 205 and MHRA/CHM advice p. 204

Co-codamol 8/500 (Non-proprietary) ^(PoM)

Tablets, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol 500 mg), net price 30-tab pack = £1.02, 32-tab pack = 50p, 100-tab pack = £3.40. Label: 29, 30

Dose

Short-term treatment of acute moderate pain


- **By mouth**

Child 12–18 years 1–2 tablets every 6 hours when necessary; max. 8 tablets daily; max. 3 days

1. Can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances.

2. Can be sold to the public under certain circumstances; for exemptions see *Medicines, Ethics and Practice*, London, Pharmaceutical Press (always consult latest edition)

Effervescent or dispersible tablets, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol 500 mg), net price 32-tab pack = £2.26, 100-tab pack = £7.06. Label: 13, 29, 30

Brands include *Paracodol* 

Note The Drug Tariff allows tablets of co-codamol labelled 'dispersible' to be dispensed against an order for 'effervescent' and *vice versa*

Dose

Short-term treatment of acute moderate pain

- By mouth

Child 12–18 years 1–2 tablets in water every 6 hours when necessary; max. 8 tablets daily; max. 3 days

Capsules, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol 500 mg), net price 10-cap pack = £1.29, 20-cap pack = £1.71. Label: 29, 30

Brands include *Paracodol* 

Dose

Short-term treatment of acute moderate pain

- By mouth

Child 12–18 years 1–2 capsules every 6 hours when necessary; max. 8 capsules daily; max. 3 days

With codeine phosphate 15 mg

When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and **no strength is stated**, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate **8 mg** and paracetamol **500 mg** should be dispensed (see preparations above).

See warnings and notes p. 200

For prescribing information on codeine, see p. 205 and MHRA/CHM advice p. 204

Codipar® (AMCo) 

Tablets, co-codamol 15/500 (codeine phosphate 15 mg, paracetamol 500 mg), net price 100-tab pack = £8.25. Label: 2, 29, 30

Dose

Short-term treatment of acute moderate pain

- By mouth

Child 12–18 years 1–2 tablets every 6 hours when necessary; max. 8 tablets daily; max. 3 days

Capsules, co-codamol 15/500 (codeine phosphate 15 mg, paracetamol 500 mg), net price 100-cap pack = £8.25. Label: 2, 29, 30

Dose

Short-term treatment of acute moderate pain

- By mouth

Child 12–18 years 1–2 capsules every 6 hours when necessary; max. 8 capsules daily; max. 3 days

Kapake® (Galen) 

Tablets, co-codamol 15/500 (codeine phosphate 15 mg, paracetamol 500 mg), net price 100-tab pack = £7.01. Label: 2, 29, 30

Dose

Short-term treatment of acute moderate pain

- By mouth

Child 12–16 years 1 tablet every 6 hours when necessary; max. 4 tablets daily; max. 3 days


Child 16–18 years 2 tablets every 6 hours when necessary; max. 8 tablets daily; max. 3 days

With codeine phosphate 30 mg

When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and **no strength is stated**, tablets, dispersible (or effervescent) tablets, or capsules, respectively containing codeine phosphate **8 mg** and paracetamol **500 mg** should be dispensed (see preparations above).

See warnings and notes p. 200

For prescribing information on codeine, see p. 205 and MHRA/CHM advice p. 204

Co-codamol 30/500 (Non-proprietary) 

Tablets (and caplets), co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-tab pack = £4.40. Label: 2, 29, 30

Brands include *Kapake*®, *Solpadol*®, *Zapain*®

Dose

Short-term treatment of acute moderate pain

- By mouth

Child 12–18 years 1–2 tablets every 6 hours when necessary; max. 8 tablets daily; max. 3 days

Capsules, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-cap pack = £4.02. Label: 2, 29, 30

Brands include *Kapake*®, *Medocodene*®, *Solpadol*®, *Tylex*®, *Zapain*®

Dose

Short-term treatment of acute moderate pain

- By mouth

Child 12–18 years 1–2 capsules every 6 hours when necessary; max. 8 capsules daily; max. 3 days

Effervescent tablets, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-tab pack = £8.19. Label: 2, 13, 29, 30

Brands include *Medocodene*® *Effervescent* (contains Na⁺ 13.6 mmol/tablet), *Solpadol*® *Effervescent* (contains Na⁺ 16.9 mmol/tablet), *Tylex*® *Effervescent* (contains Na⁺ 14.2 mmol/tablet)

Dose

Short-term treatment of acute moderate pain

- By mouth

Child 12–18 years 1–2 tablets in water every 6 hours when necessary; max. 8 tablets daily; max. 3 days

With dihydrocodeine tartrate 10 mg

When co-dydramol tablets are prescribed and **no strength is stated**, tablets containing dihydrocodeine tartrate **10 mg** and paracetamol **500 mg** should be dispensed.

See warnings and notes on p. 200

For prescribing information on dihydrocodeine, see p. 206

Co-dydramol (Non-proprietary) 

Tablets, co-dydramol 10/500 (dihydrocodeine tartrate 10 mg, paracetamol 500 mg), net price 30-tab pack = 98p. Label: 29, 30

Dose

Mild to moderate pain

- By mouth


Child 12–18 years 1–2 tablets every 4–6 hours; max. 8 tablets daily

With dihydrocodeine tartrate 20 mg

When co-dydramol tablets are prescribed and **no strength is stated**, tablets containing dihydrocodeine tartrate **10 mg** and paracetamol **500 mg** should be dispensed (see preparation above).

See warnings and notes on p. 200

For prescribing information on dihydrocodeine, see p. 206

Remedeine® (Crescent) 

Tablets, paracetamol 500 mg, dihydrocodeine tartrate 20 mg, net price 112-tab pack = £11.13. Label: 2, 29, 30

Dose

Severe pain

● By mouth

Child 12–18 years 1–2 tablets every 4–6 hours; max. 8 tablets daily

■ With dihydrocodeine tartrate 30 mg

When co-dydramol tablets are prescribed and **no strength is stated**, tablets containing dihydrocodeine tartrate **10 mg** and paracetamol **500 mg** should be dispensed (see preparation above).

See warnings and notes on p. 200

For prescribing information on dihydrocodeine, see p. 206

Remedeine Forte® (Crescent) (PoM) 

Tablets, paracetamol 500 mg, dihydrocodeine tartrate 30 mg, net price 56-tab pack = £6.82. Label: 2, 29, 30

Dose

Severe pain

● By mouth

Child 12–18 years 1–2 tablets every 4–6 hours; max. 8 tablets daily

■ With tramadol

For prescribing information on tramadol, see section 4.7.2

Tramacet® (Grünenthal) (PoM)

Tablets, f/c, yellow, tramadol hydrochloride 37.5 mg, paracetamol 325 mg, net price 60-tab pack = £9.68. Label: 2, 25, 29, 30

Dose

Moderate to severe pain

● By mouth

Child 12–18 years 2 tablets not more often than every 6 hours; max. 8 tablets daily

Effervescent tablets, pink, tramadol hydrochloride 37.5 mg, paracetamol 325 mg, net price 60-tab pack = £9.68. Label: 2, 13, 29, 30

Electrolytes Na⁺ 7.8 mmol/tablet

Dose

Moderate to severe pain

● By mouth

Child 12–18 years 2 tablets not more often than every 6 hours; max. 8 tablets daily

■ With antiemetics

For prescribing information on codeine phosphate, see Codeine Phosphate, section 4.7.2.

Migravele® (McNeil) 

Tablets, all f/c, *pink tablets*, buclizine hydrochloride 6.25 mg, paracetamol 500 mg, codeine phosphate 8 mg; *yellow tablets*, paracetamol 500 mg, codeine phosphate 8 mg, net price 48-tab *Migravele* (PoM) (32 pink + 16 yellow) = £3.64; 48 pink (*Migravele Pink*) = £3.97. Label: 2, (*Migravele Pink*), 17, 30

Dose

Treatment of acute migraine

● By mouth

Child 12–14 years 1 pink tablet at onset of attack, or if it is imminent, then 1 yellow tablet every 4 hours if necessary; max. 1 pink and 3 yellow tablets in 24 hours

Child 15–18 years 2 pink tablets at onset of attack, or if it is imminent, then 2 yellow tablets every 4 hours if necessary; max. 2 pink and 6 yellow tablets in 24 hours

4.7.2 Opioid analgesics

Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause tolerance, but this is no deterrent in the control of pain in terminal illness, for guidelines see Pain Management with Opioids, (p. 16). Regular use of a potent opioid may be appropriate for certain cases of chronic non-malignant pain; treatment should be supervised by a specialist and the child should be assessed at regular intervals.

Cautions Opioids should be used with caution in children with impaired respiratory function and asthma (avoid during an acute attack), hypotension, shock, myasthenia gravis, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders. A reduced dose is recommended in hypothyroidism or adrenocortical insufficiency. Repeated use of opioid analgesics is associated with the development of psychological and physical dependence; although this is rarely a problem with therapeutic use, caution is advised if prescribing for patients with a history of drug dependence. Avoid abrupt withdrawal after long-term treatment. Transdermal preparations (fentanyl or buprenorphine patches) are not suitable for acute pain or in those children whose analgesic requirements are changing rapidly, because the long time to steady state prevents rapid titration of the dose.

Palliative care In the control of pain in terminal illness, the cautions listed above should not necessarily be a deterrent to the use of opioid analgesics.

Contra-indications Opioid analgesics should be avoided in children with acute respiratory depression, and when there is a risk of paralytic ileus. They are also contra-indicated in conditions associated with raised intracranial pressure, and in head injury (opioid analgesics interfere with pupillary responses vital for neurological assessment). Comatose children should not be treated with opioid analgesics.

Hepatic impairment Opioid analgesics may precipitate coma in children with hepatic impairment; avoid use or reduce dose.

Renal impairment The effects of opioid analgesia are increased and prolonged and there is increased cerebral sensitivity when children with renal impairment are treated with opioid analgesics; avoid use or reduce dose.

Pregnancy Respiratory depression and withdrawal symptoms can occur in the neonate if opioid analgesics are used during delivery; also gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labour.

Side-effects Opioid analgesics share many side-effects, although qualitative and quantitative differences exist. The most common side-effects include nausea and vomiting (particularly in initial stages), constipation, dry mouth and biliary spasm; larger doses produce muscle rigidity, hypotension and respiratory depression (for reversal of opioid-induced respiratory depression, see section 15.1.7); neonates, particularly if preterm, may be more susceptible. Other common side-effects of opioid analgesics include bradycardia, tachycardia, palpitation, oedema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, mood changes, dependence, dizziness, confusion, drowsiness, sleep distur-

bances, headache, sexual dysfunction, difficulty with micturition, urinary retention, ureteric spasm, miosis, visual disturbances, sweating, flushing, rash, urticaria, and pruritus. **Overdosage:** see Emergency Treatment of Poisoning, p. 27.

Long-term use of opioid analgesics can lead to hypogonadism and adrenal insufficiency in both boys and girls. This is thought to be dose related and can lead to amenorrhoea, reduced libido, infertility, depression, and erectile dysfunction. Long-term use of opioid analgesics has also been associated with a state of abnormal pain sensitivity (hyperalgesia). Pain associated with hyperalgesia is usually distinct from pain associated with disease progression or breakthrough pain, and is often more diffuse and less defined. Treatment of hyperalgesia involves reducing the dose of opioid medication or switching therapy; cases of suspected hyperalgesia should be referred to a specialist pain team.

Interactions See Appendix 1 (opioid analgesics) (**important:** special hazard with *pethidine* and possibly other opioids and MAOIs).

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced. Driving at the start of therapy with opioid analgesics, and following dose changes, should be avoided.

Strong opioids Morphine remains the most valuable opioid analgesic for severe pain although it frequently causes nausea and vomiting. It is the standard against which other opioid analgesics are compared. In addition to relief of pain, morphine also confers a state of euphoria and mental detachment.

Morphine is the opioid of choice for the oral treatment of severe pain in palliative care. It is given regularly every 4 hours (or every 12 or 24 hours as modified-release preparations). For guidelines on dosage adjustment in palliative care, see Pain Management with Opioids, (p. 16).

Buprenorphine has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in children dependent on other opioids. It has abuse potential and may itself cause dependence. It has a much longer duration of action than morphine and sublingually is an effective analgesic for 6 to 8 hours. Unlike most opioid analgesics, the effects of buprenorphine are only partially reversed by naloxone. It is used rarely in children.

Diamorphine (heroin) is a powerful opioid analgesic. It may cause less nausea and hypotension than morphine. In palliative care the greater solubility of diamorphine allows effective doses to be injected in smaller volumes and this is important in the emaciated child.

Diamorphine is sometimes given by the intranasal route to treat acute pain in children, for example, in accident and emergency units; however, as yet, there is limited safety and efficacy data to support this practice.

Alfentanil, fentanyl and remifentanyl are used by injection for intra-operative analgesia (section 15.1.4.3). Fentanyl is available in a transdermal drug delivery system as a self-adhesive patch which is changed every 72 hours.

Methadone is less sedating than morphine and acts for longer periods. In prolonged use, methadone should not be administered more often than twice daily to avoid the risk of accumulation and opioid overdose. Methadone may be used instead of morphine when excitation (or

exacerbation of pain) occurs with morphine. Methadone may also be used to treat children with neonatal abstinence syndrome (section 4.10).

Papaveretum should not be used in children; morphine is easier to prescribe and less prone to error with regard to the strength and dose.

Pethidine produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high doses is a less potent analgesic. Its use in children is not recommended. Pethidine is used for analgesia in labour; however, other opioids, such as morphine or diamorphine, are often preferred for obstetric pain.

Tramadol is used in older children and produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. It has fewer of the typical opioid side-effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported.

Weak opioids Codeine can be used for the relief of short-term acute moderate pain in children older than 12 years where other painkillers such as paracetamol or ibuprofen have proved ineffective, but see Variation in Metabolism, p. 205

MHRA/CHM advice

Codeine for analgesia: restricted use in children due to reports of morphine toxicity (July 2013)

Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen alone. A significant risk of serious and life-threatening adverse reactions has been identified in children with obstructive sleep apnoea who received codeine after tonsillectomy or adenoidectomy:

- in children aged 12–18 years, the maximum daily dose of codeine should not exceed 240 mg. Doses may be taken up to four times a day at intervals of no less than 6 hours. The lowest effective dose should be used and duration of treatment should be limited to 3 days
- codeine is contra-indicated in all children (under 18 years) who undergo the removal of tonsils or adenoids for the treatment of obstructive sleep apnoea
- codeine is not recommended for use in children whose breathing may be compromised, including those with neuromuscular disorders, severe cardiac or respiratory conditions, respiratory infections, multiple trauma or extensive surgical procedures
- codeine is contra-indicated in patients of any age who are known to be ultra-rapid metabolisers of codeine (CYP2D6 ultra-rapid metabolisers)
- codeine should not be used in breast-feeding mothers because it can pass to the baby through breast milk
- parents and carers should be advised on how to recognise signs and symptoms of morphine toxicity, and to stop treatment and seek medical attention if signs or symptoms of toxicity occur (including reduced consciousness, lack of appetite, somnolence, constipation, respiratory depression, 'pin-point' pupils, nausea, vomiting)

Dihydrocodeine has an analgesic efficacy similar to that of codeine.

Dose Doses of opioids may need to be adjusted individually according to the degree of analgesia and side-effects; response to opioids varies widely, particularly in the neonatal period. Opioid overdose can have serious consequences and the dose should be calculated and checked with care.

Postoperative analgesia A combination of opioid and non-opioid analgesics is used to treat postoperative pain (section 15.1.4.2). The use of intra-operative opioids affects the prescribing of postoperative analgesics. A postoperative opioid analgesic should be given with care since it may potentiate any residual respiratory depression (for the treatment of opioid-induced respiratory depression, see section 15.1.7).

Morphine is used most widely. **Tramadol** is not as effective in severe pain as other opioid analgesics. **Buprenorphine** may antagonise the analgesic effect of previously administered opioids and is generally not recommended. **Pethidine** is unsuitable for postoperative pain because it is metabolised to norpethidine which may accumulate, particularly in neonates and in renal impairment; norpethidine stimulates the central nervous system and may cause convulsions.

Opioids are also given epidurally [unlicensed route] in the postoperative period but are associated with side-effects such as pruritus, urinary retention, nausea and vomiting; respiratory depression can be delayed, particularly with morphine.

For details of patient-controlled analgesia (PCA) and nurse-controlled analgesia (NCA) to relieve postoperative pain, consult hospital protocols.

Dental and orofacial pain Opioid analgesics are relatively ineffective in dental pain. Like other opioids, **dihydrocodeine** often causes nausea and vomiting which limits its value in dental pain; if taken for more than a few doses it is also liable to cause constipation. Dihydrocodeine is not very effective in postoperative dental pain.

For the management of dental and orofacial pain, see p. 199.

Pain management and opioid dependence

Although caution is necessary, patients who are dependent on opioids or have a history of drug dependence may be treated with opioid analgesics when there is a clinical need. Treatment with opioid analgesics in this patient group should normally be carried out with the advice of specialists. However, doctors do not require a special licence to prescribe opioid analgesics to patients with opioid dependence for relief of pain due to organic disease or injury.

Dependence and withdrawal Psychological dependence rarely occurs when opioids are used for pain relief but tolerance can develop during long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. For information on the treatment of neonatal abstinence syndrome, see section 4.10.

BUPRENORPHINE

Cautions see notes above; also impaired consciousness; effects only partially reversed by naloxone; monitor liver function

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding present in low levels in breast milk—monitor neonate for drowsiness, adequate weight gain, and developmental milestones

Side-effects see notes above; can induce mild withdrawal symptoms in children dependent on opioids;

also diarrhoea, abdominal pain, anorexia, dyspepsia; vasodilatation; dyspnoea; paraesthesia, asthenia, fatigue, agitation, anxiety; *less commonly* flatulence, taste disturbance, hypertension, syncope, hypoxia, wheezing, cough, restlessness, depersonalisation, dysarthria, impaired memory, hypoaesthesia, tremor, influenza-like symptoms, pyrexia, rhinitis, rigors, muscle cramp, myalgia, tinnitus, dry eye, and dry skin; *rarely* paralytic ileus, dysphagia, diverticulitis, impaired concentration, and psychosis; *very rarely* retching, hyperventilation, hiccups, and muscle fasciculation; hepatic necrosis and hepatitis also reported

Licensed use sublingual tablets not licensed for use in children under 6 years; injection not licensed for use in children under 6 months

Indications and dose

Moderate to severe pain

• By sublingual administration

Child body-weight 16–25 kg 100 micrograms every 6–8 hours

Child body-weight 25–37.5 kg 100–200 micrograms every 6–8 hours

Child body-weight 37.5–50 kg 200–300 micrograms every 6–8 hours

Child body-weight over 50 kg 200–400 micrograms every 6–8 hours

• By intramuscular or by slow intravenous injection

Child 6 months–12 years 3–6 micrograms/kg every 6–8 hours, max. 9 micrograms/kg

Child 12–18 years 300–600 micrograms every 6–8 hours

Administration for administration *by mouth*, tablets may be halved

Temgesic® (Reckitt Benckiser) CD3

Tablets (sublingual), buprenorphine (as hydrochloride), 200 micrograms, net price 50-tab pack = £5.04; 400 micrograms, 50-tab pack = £10.07. Label: 2, 26

Injection, buprenorphine (as hydrochloride) 300 micrograms/mL, net price 1-mL amp = 49p

CODEINE PHOSPHATE

Cautions see notes above and MHRA/CHM advice; also cardiac arrhythmias; acute abdomen; gallstones
Variation in metabolism The capacity to metabolise codeine to morphine can vary considerably between children; there is a marked increase in morphine toxicity in children who are ultra-rapid codeine metabolisers (CYP2D6 ultra-rapid metabolisers) and a reduced therapeutic effect in poor codeine metabolisers

Contra-indications see notes above; also in children under 18 years who undergo the removal of tonsils or adenoids for the treatment of obstructive sleep apnoea; known ultra-rapid codeine metabolisers (see Variation in Metabolism above)

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding Avoid—although amount usually too small to be harmful, mothers vary considerably in their capacity to metabolise codeine—risk of morphine overdose in infant

Side-effects see notes above; also abdominal pain, anorexia, seizures, malaise, hypothermia, antidiuretic

effect, and muscle fasciculation; pancreatitis also reported

Indications and dose

Short-term treatment of acute moderate pain

- By mouth or by intramuscular injection

Child 12–18 years 30–60 mg every 6 hours when necessary; max. 240 mg daily; max. 3 days

Codeine Phosphate (Non-proprietary)

Tablets ^(PoM), codeine phosphate 15 mg, net price 28-tab pack = £1.17; 30 mg, 28-tab pack = £1.33; 60 mg, 28-tab pack = £3.04. Label: 2

Syrup ^(PoM), codeine phosphate 25 mg/5 mL, net price 100 mL = 93p. Label: 2

Injection ^(CD2), codeine phosphate 60 mg/mL, net price 1-mL amp = £2.37

With paracetamol

Section 4.7.1

DIAMORPHINE HYDROCHLORIDE (Heroin Hydrochloride)

Cautions see notes above; also severe diarrhoea; toxic psychosis, CNS depression; severe cor pulmonale

Contra-indications see notes above; also delayed gastric emptying; phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding therapeutic doses unlikely to affect infant; withdrawal symptoms in infants of dependent mothers; breast-feeding not best method of treating dependence in offspring

Side-effects see notes above; also anorexia, taste disturbance; syncope; asthenia, raised intracranial pressure; myocardial infarction also reported

Licensed use intranasal route not licensed

Indications and dose

Acute or chronic pain

- By mouth

Child 1 month–12 years 100–200 micrograms/kg (max. 10 mg) every 4 hours, adjusted according to response

Child 12–18 years 5–10 mg every 4 hours, adjusted according to response

- By intravenous administration

Neonate (ventilated) initially by intravenous injection over 30 minutes, 50 micrograms/kg then by continuous intravenous infusion, 15 micrograms/kg/hour, adjusted according to response

Neonate (non-ventilated) by continuous intravenous infusion 2.5–7 micrograms/kg/hour, adjusted according to response

Child 1 month–12 years by continuous intravenous infusion 12.5–25 micrograms/kg/hour, adjusted according to response

- By intravenous injection

Child 1–3 months 20 micrograms/kg every 6 hours, adjusted according to response

Child 3–6 months 25–50 micrograms/kg every 6 hours, adjusted according to response

Child 6–12 months 75 micrograms/kg every 4 hours, adjusted according to response

Child 1–12 years 75–100 micrograms/kg (max. 5 mg) every 4 hours, adjusted according to response

Child 12–18 years 2.5–5 mg every 4 hours, adjusted according to response

- By continuous subcutaneous infusion

See Continuous Subcutaneous Infusions, in Palliative care, (p. 19)

- By subcutaneous or by intramuscular injection

Child 12–18 years 5 mg every 4 hours, adjusted according to response

Acute pain in an emergency setting; short painful procedures

- Intranasally (but see p. 204)

Child over 10 kg 100 micrograms/kg, max. 10 mg

Administration for intravenous infusion, dilute in Glucose 5% or Sodium Chloride 0.9%; Glucose 5% is preferable

For intranasal administration, diamorphine powder should be dissolved in sufficient volume of Water for Injections to provide the requisite dose in 0.2 mL of solution; use solution immediately after preparation

Diamorphine (Non-proprietary) ^(CD2)

Tablets, diamorphine hydrochloride 10 mg, net price 100-tab pack = £23.00. Label: 2

Injection, powder for reconstitution, diamorphine hydrochloride, net price 5-mg amp = £2.27, 10-mg amp = £2.57, 30-mg amp = £2.84, 100-mg amp = £8.46, 500-mg amp = £37.49

DIHYDROCODEINE TARTRATE

Cautions see notes above; also pancreatitis; severe cor pulmonale

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding use only if potential benefit outweighs risk

Side-effects see notes above; also paralytic ileus, abdominal pain, diarrhoea, seizures, and paraesthesia

Licensed use most preparations not licensed for use in children under 4 years

Indications and dose

Moderate to severe pain

- By mouth or by intramuscular injection or by subcutaneous injection

Child 1–4 years 500 micrograms/kg every 4–6 hours

Child 4–12 years 0.5–1 mg/kg (max. 30 mg) every 4–6 hours

Child 12–18 years 30 mg (max. 50 mg by intramuscular or deep subcutaneous injection) every 4–6 hours

Dihydrocodeine (Non-proprietary)

Tablets ^(PoM), dihydrocodeine tartrate 30 mg, net price 28-tab pack = £1.15. Label: 2

Dental prescribing on NHS Dihydrocodeine Tablets 30 mg may be prescribed

Oral solution ^(PoM), dihydrocodeine tartrate 10 mg/5 mL, net price 150 mL = £6.20. Label: 2

Injection ^(CD2), dihydrocodeine tartrate 50 mg/mL, net price 1-mL amp = £7.89

DF 118 Forte® (Martindale) [PoM]

Tablets, dihydrocodeine tartrate 40 mg, net price 100-tab pack = £11.51. Label: 2

Dose**Severe pain**

- **By mouth**
Child 12–18 years 40–80 mg 3 times daily; max. 240 mg daily

■ **Modified release****DHC Continus®** (Napp) [PoM]

Tablets, m/r, dihydrocodeine tartrate 60 mg, net price 56-tab pack = £5.20; 90 mg, 56-tab pack = £8.66; 120 mg, 56-tab pack = £10.95. Label: 2, 25

Dose**Chronic severe pain**

- **By mouth**
Child 12–18 years 60–120 mg every 12 hours

■ **With paracetamol**

Section 4.7.1

FENTANYL

Cautions see notes above; also diabetes mellitus, impaired consciousness, cerebral tumour, see also Transdermal Fentanyl, below

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding monitor infant for opioid-induced side-effects

Side-effects see notes above; also abdominal pain, dyspepsia, diarrhoea, gastro-oesophageal reflux disease, stomatitis, anorexia, hypertension, vasodilatation, dyspnoea, aesthenia, myoclonus, anxiety, tremor, appetite changes, rhinitis, pharyngitis, paraesthesia, application-site reactions; *less commonly* ileus, flatulence, hypoventilation, impaired concentration, impaired coordination, amnesia, speech disorder, malaise, seizure, dysgeusia, parosmia, pyrexia, thirst, blood disorders (including thrombocytopenia), arthralgia, chills; *rarely* hiccups, *very rarely* arrhythmia, apnoea, haemoptysis, ataxia, delusions, bladder pain

Indications and dose**Severe chronic pain**

- **By transdermal route**

Child 2–16 years currently treated with strong opioid analgesic, initial dose based on previous 24-hour opioid requirement (consult product literature)

Child 16–18 years child not currently treated with strong opioid analgesic (but see Transdermal Fentanyl, below), one '12' or '25 micrograms/hour' patch replaced after 72 hours; **child currently treated** with strong opioid analgesic, initial dose based on previous 24-hour opioid requirement (consult product literature)

Dose adjustment When starting, evaluation of the analgesic effect should **not** be made before the system has been worn for **24 hours** (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from time of first patch application; if necessary dose should be adjusted at 48–72-hour intervals in steps of 12–25 micrograms/hour. More than one patch may be used at a time (but applied at *same time* to avoid confusion)—consider additional or alternative analgesic therapy if

dose required exceeds 300 micrograms/hour (**important:** it takes 17 hours or more for the plasma-fentanyl concentration to decrease by 50%—replacement opioid therapy should be initiated at a low dose and increased gradually).

Long duration of action In view of the long duration of action, children who have had severe side-effects should be monitored for up to 24 hours after patch removal

Breakthrough pain and premedication analgesia, see under preparation below

Peri-operative analgesia section 15.1.4.3

Conversion (from long-term oral morphine to transdermal fentanyl), see Pain Management with Opioids, (p. 16)

Administration For *patches*, apply to dry, non-irritated, non-irradiated, non-hairy skin on torso or upper arm, removing after 72 hours and siting replacement patch on a different area (avoid using the same area for several days).

■ **Lozenges****Actiq®** (Flynn) [CD2]

Lozenge, (with oromucosal applicator), fentanyl (as citrate) 200 micrograms, net price 3 = £21.05, 30 = £210.41; 400 micrograms, 3 = £21.05, 30 = £210.41; 600 micrograms, 3 = £21.05, 30 = £210.41; 800 micrograms, 3 = £21.05, 30 = £210.41; 1.2 mg, 3 = £21.05, 30 = £210.41; 1.6 mg, 3 = £21.05, 30 = £210.41. Label: 2

Dose**Breakthrough pain**

- **By transmucosal application** (lozenge with oromucosal applicator)

Child 16–18 years initially 200 micrograms (over 15 minutes) repeated if necessary 15 minutes after first dose (no more than 2 dose units for each pain episode); if adequate pain relief not achieved with 1 dose unit for consecutive breakthrough pain episodes, increase the strength of the dose unit until adequate pain relief achieved with 4 lozenges or less daily

Note If more than 4 episodes of breakthrough pain each day, adjust dose of background analgesic

■ **Patches****Transdermal fentanyl**

Fever or external heat Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat, for example a hot bath or sauna (may also increase absorption)

Respiratory depression Risk of fatal respiratory depression, particularly in patients not previously treated with a strong opioid analgesic; manufacturer recommends use only in opioid tolerant patients

Counselling Patients and carers should be informed about safe use, including correct administration and disposal, strict adherence to dosage instructions, and the symptoms and signs of opioid overdose. Patches should be removed immediately in case of breathing difficulties, marked drowsiness, confusion, dizziness, or impaired speech, and patients and carers should seek prompt medical attention.

Prescriptions Prescriptions for fentanyl patches can be written to show the strength in terms of the release rate and it is acceptable to write '*Fentanyl 25 patches*' to prescribe patches that release fentanyl 25 micrograms per hour. The dosage should be expressed in terms of the interval between applying a patch and replacing it with a new one, e.g. '*one patch to be applied every 72 hours*'. The total quantity of patches should be written in words and figures.

Fentanyl (Non-proprietary) (CD2)

Patches, self-adhesive, fentanyl, '12' patch (releasing approx. 12 micrograms/hour for 72 hours), net price 5 = £12.59; '25' patch (releasing approx. 25 micrograms/hour for 72 hours), 5 = £17.99; '37.5' patch (releasing approx. 37.5 micrograms/hour for 72 hours; *Mezolar*® brand only), 5 = £15.46; '50' patch (releasing approx. 50 micrograms/hour for 72 hours), 5 = £33.66; '75' patch (releasing approx. 75 micrograms/hour for 72 hours), 5 = £46.99; '100' patch (releasing approx. 100 micrograms/hour for 72 hours), 5 = £57.86. Label: 2, counselling, administration

Brands include *Fencino*®, *Fentalis*®, *Matrifan*®, *Mezolar*®, *Opiodur*®, *Osmantil*®, *Tilofyl*®, *Victanyl*®

Durogesic DTrans® (Janssen) (CD2)

Patches, self-adhesive, transparent, fentanyl, '12' patch (releasing approx. 12 micrograms/hour for 72 hours), net price 5 = £12.59; '25' patch (releasing approx. 25 micrograms/hour for 72 hours), 5 = £17.99; '50' patch (releasing approx. 50 micrograms/hour for 72 hours), 5 = £33.66; '75' patch (releasing approx. 75 micrograms/hour for 72 hours), 5 = £46.99; '100' patch (releasing approx. 100 micrograms/hour for 72 hours), 5 = £57.86. Label: 2, counselling, administration

HYDROMORPHONE HYDROCHLORIDE

Cautions see notes above; also pancreatitis; toxic psychosis

Contra-indications see notes above; also acute abdomen

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding avoid—no information available

Side-effects see notes above; also abdominal pain, anorexia, anxiety; *less commonly* diarrhoea, paralytic ileus, peripheral oedema, dysgeusia, seizures, paraesthesia, dyskinesia, myoclonus, agitation, tremor

Indications and dose**Severe pain in cancer**

• By mouth

Child 12–18 years 1.3 mg every 4 hours, increased if necessary according to severity of pain

Administration Swallow whole capsule or sprinkle contents on soft food

Palladone® (Napp) (CD2)

Capsules, hydromorphone hydrochloride 1.3 mg (orange/clear), net price 56-cap pack = £8.82; 2.6 mg (red/clear), 56-cap pack = £17.64. Label: 2, counselling, see below

■ **Modified release****Palladone**® SR (Napp) (CD2)

Capsules, m/r, hydromorphone hydrochloride 2 mg (yellow/clear), net price 56-cap pack = £20.98; 4 mg (pale blue/clear), 56-cap pack = £28.75; 8 mg (pink/clear), 56-cap pack = £56.08; 16 mg (brown/clear), 56-cap pack = £106.53; 24 mg (dark blue/clear), 56-cap pack = £159.82. Label: 2, counselling, see below

Dose**Severe pain in cancer**

• By mouth

Child 12–18 years 4 mg every 12 hours, increased if necessary according to severity of pain

Counselling Swallow whole or open capsule and sprinkle contents on soft cold food (swallow the pellets within the capsule whole; do not crush or chew)

METHADONE HYDROCHLORIDE

Cautions see notes above; also history of cardiac conduction abnormalities, family history of sudden death (ECG monitoring recommended; see also QT-interval prolongation, below)

QT-interval prolongation Children with the following risk factors for QT-interval prolongation should be carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval; children requiring more than 100 mg daily should also be monitored

Contra-indications see notes above; also phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding withdrawal symptoms in infant; breast-feeding permissible during maintenance but dose should be as low as possible and infant monitored to avoid sedation

Side-effects see notes above; also QT-interval prolongation; torsade de pointes, hypothermia, restlessness, raised intracranial pressure, dysmenorrhoea, dry eyes, and hyperprolactinaemia

Licensed use not licensed for use in children

Indications and dose

Neonatal opioid withdrawal dose may vary, consult local guidelines

• By mouth

Neonate initially 100 micrograms/kg increased by 50 micrograms/kg every 6 hours until symptoms are controlled; for maintenance, total daily dose that controls symptoms given in 2 divided doses; to withdraw, reduce dose over 7–10 days

Methadone (Non-proprietary) (CD2)

Oral solution 1 mg/mL, methadone hydrochloride 1 mg/mL, net price 30 mL = 62p, 50 mL = £1.04, 100 mL = £2.08, 500 mL = £6.35. Label: 2

Brands include *Eptadone*®, *Metharose*® (sugar-free), *Physeptone* (also as sugar-free)

Safe Practice

This preparation is 2½ times the strength of Methadone Linctus; many preparations of this strength are licensed for opioid dependence only but some are also licensed for analgesia in severe pain

MORPHINE SALTS

Cautions see notes above; also pancreatitis, cardiac arrhythmias, severe cor pulmonale

Contra-indications see notes above; also delayed gastric emptying, acute abdomen; heart failure secondary to chronic lung disease; phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding therapeutic doses unlikely to affect infant

Side-effects see notes above; also paralytic ileus, abdominal pain, anorexia, dyspepsia, exacerbation of pancreatitis, taste disturbance, hypertension, hypothermia, syncope, bronchospasm, inhibition of cough reflex, restlessness, seizures, paraesthesia, asthenia, malaise, disorientation, excitation, agitation, delirium, raised intracranial pressure, amenorrhoea, myoclonus, muscle fasciculation, rhabdomyolysis, nystagmus

Licensed use *Oramorph*[®] solution not licensed for use in children under 1 year; *Oramorph*[®] unit dose vials not licensed for use in children under 6 years; *Sevredol*[®] tablets not licensed for use in children under 3 years; *Filnarine*[®] SR tablets not licensed for use in children under 6 years; *MST Continus*[®] preparations licensed to treat children with cancer pain (age-range not specified by manufacturer); *MXL*[®] capsules not licensed for use in children under 1 year; suppositories not licensed for use in children

Indications and dose

Pain

• By subcutaneous injection

Neonate initially 100 micrograms/kg every 6 hours, adjusted according to response

Child 1–6 months initially 100–200 micrograms/kg every 6 hours, adjusted according to response

Child 6 months–2 years initially 100–200 micrograms/kg every 4 hours, adjusted according to response

Child 2–12 years initially 200 micrograms/kg every 4 hours, adjusted according to response

Child 12–18 years initially 2.5–10 mg every 4 hours, adjusted according to response

• By intravenous injection over at least 5 minutes

Neonate initially 50 micrograms/kg every 6 hours, adjusted according to response

Child 1–6 months initially 100 micrograms/kg every 6 hours, adjusted according to response

Child 6 months–12 years initially 100 micrograms/kg every 4 hours, adjusted according to response

Child 12–18 years initially 5 mg every 4 hours, adjusted according to response

• By intravenous administration

Neonate initially by intravenous injection (over at least 5 minutes) 50 micrograms/kg then by continuous intravenous infusion 5–20 micrograms/kg/hour adjusted according to response

Child 1–6 months initially by intravenous injection (over at least 5 minutes) 100 micrograms/kg then by continuous intravenous infusion 10–30 micrograms/kg/hour adjusted according to response

Child 6 months–12 years initially by intravenous injection (over at least 5 minutes) 100 micrograms/kg then by continuous intravenous infusion 20–30 micrograms/kg/hour adjusted according to response

Child 12–18 years initially by intravenous injection (over at least 5 minutes) 5 mg then by continuous intravenous infusion 20–30 micrograms/kg/hour adjusted according to response

• By mouth or by rectum

Child 1–3 months initially 50–100 micrograms/kg every 4 hours, adjusted according to response

Child 3–6 months 100–150 micrograms/kg every 4 hours, adjusted according to response

Child 6–12 months 200 micrograms/kg every 4 hours, adjusted according to response

Child 1–2 years initially 200–300 micrograms/kg every 4 hours, adjusted according to response

Child 2–12 years initially 200–300 micrograms/kg (max. 10 mg) every 4 hours, adjusted according to response

Child 12–18 years initially 5–10 mg every 4 hours, adjusted according to response

• By continuous subcutaneous infusion

Child 1–3 months 10 micrograms/kg/hour, adjusted according to response

Child 3 months–18 years 20 micrograms/kg/hour, adjusted according to response

Neonatal opioid withdrawal under specialist supervision

• By mouth

Neonate initially 40 micrograms/kg every 4 hours until symptoms controlled, increase dose if necessary; reduce frequency gradually over 6–10 days, and stop when 40 micrograms/kg once daily achieved; dose may vary, consult local guidelines

Administration for continuous intravenous infusion, dilute with Glucose 5% or 10% or Sodium Chloride 0.9%

Neonatal intensive care, dilute 2.5 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 micrograms/kg/hour

Oral solutions

Note For advice on transfer from oral solutions of morphine to modified-release preparations of morphine, see Pain Management with Opioids, (p. 16)

Morphine Oral Solutions

(^{PM}) or (^{CD2})

Oral solutions of morphine can be prescribed by writing the formula:

Morphine hydrochloride 5 mg
Chloroform water to 5 mL

Note The proportion of morphine hydrochloride may be altered when specified by the prescriber; if above 13 mg per 5 mL the solution becomes (^{CD2}). For sample prescription see Controlled Drugs and Drug Dependence, p. 8. It is usual to adjust the strength so that the dose volume is 5 or 10 mL.

Oramorph[®] (Boehringer Ingelheim)

Oramorph[®] oral solution (^{PM}), morphine sulfate 10 mg/5 mL, net price 100-mL pack = £1.89; 300-mL pack = £5.45; 500-mL pack = £8.50. Label: 2

Oramorph[®] concentrated oral solution (^{CD2}), sugar-free, morphine sulfate 100 mg/5 mL, net price 30-mL pack = £4.98; 120-mL pack = £19.50 (both with calibrated dropper). Label: 2

Tablets

Sevredol[®] (Napp) (^{CD2})

Tablets, f/c, scored, morphine sulfate 10 mg (blue), net price 56-tablet pack = £5.31; 20 mg (pink), 56-tablet pack = £10.61; 50 mg (pale green), 56-tablet pack = £28.02. Label: 2

Modified-release 12-hourly oral preparations

Filinarine® SR (Teva UK) ^(CD2)

Tablets, m/r, f/c, morphine sulfate 10 mg (pink), net price 60-tab pack = £3.30; 30 mg (blue), 60-tab pack = £7.89; 60 mg (pink), 60-tab pack = £15.39; 100 mg (white), 60-tab pack = £24.37; 200 mg (white), 60-tab pack = £48.74. Label: 2, 25

Dose

• By mouth

Every 12 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Pain Management with Opioids, (p. 16); dosage requirements should be reviewed if the brand is altered

Note Prescriptions must also specify 'tablets' (i.e. 'Filinarine SR tablets')

MST Continus® (Napp) ^(CD2)

Tablets, m/r, f/c, morphine sulfate 5 mg (white), net price 60-tab pack = £3.29; 10 mg (brown), 60-tab pack = £5.18; 15 mg (green), 60-tab pack = £9.10; 30 mg (purple), 60-tab pack = £12.47; 60 mg (orange), 60-tab pack = £24.32; 100 mg (grey), 60-tab pack = £38.50; 200 mg (green), 60-tab pack = £81.34. Label: 2, 25

Suspension (= sachet of granules to mix with water), m/r, pink, morphine sulfate 20 mg/sachet, net price 30-sachet pack = £24.58; 30 mg/sachet, 30-sachet pack = £25.54; 60 mg/sachet, 30-sachet pack = £51.09; 100 mg/sachet, 30-sachet pack = £85.15; 200 mg/sachet pack, 30-sachet pack = £170.30. Label: 2, 13

Dose

• By mouth

Every 12 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Pain Management with Opioids, (p. 16); dosage requirements should be reviewed if the brand is altered

Note Prescriptions must also specify 'tablets' or 'suspension' (i.e. 'MST Continus tablets' or 'MST Continus suspension')

Modified-release 24-hourly oral preparations

MXL® (Napp) ^(CD2)

Capsules, m/r, morphine sulfate 30 mg (light blue), net price 28-cap pack = £10.91; 60 mg (brown), 28-cap pack = £14.95; 90 mg (pink), 28-cap pack = £22.04; 120 mg (green), 28-cap pack = £29.15; 150 mg (blue), 28-cap pack = £36.43; 200 mg (red-brown), 28-cap pack = £46.15. Label: 2, counselling, see below

Dose

• By mouth

Every 24 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Pain Management with Opioids, (p. 16); dosage requirements should be reviewed if the brand is altered

Counselling Swallow whole or open capsule and sprinkle contents on soft food

Note Prescriptions must also specify 'capsules' (i.e. 'MXL capsules')

Suppositories

Morphine (Non-proprietary) ^(CD2)

Suppositories, morphine sulfate 10 mg, net price 12 = £11.21; 15 mg, 12 = £15.88; 30 mg, 12 = £17.76. Label: 2

Note Both the strength of the suppositories and the morphine salt contained in them must be specified by the prescriber

Other strengths of morphine sulfate suppositories available from 'special-order' manufacturers or specialist importing companies, see p. 840

Injections

Morphine Sulfate (Non-proprietary) ^(CD2)

Injection, morphine sulfate 10, 15, 20, and 30 mg/mL, net price 1- and 2-mL amp (all) = 72p–£4.48

Intravenous infusion, morphine sulfate 1 mg/mL, net price 50-mL vial = £5.25; 2 mg/mL, 50-mL vial = £5.89

Miniject® Morphine Sulphate (UCB Pharma) ^(CD2)

Injection, morphine sulfate 1 mg/mL, net price 10-mL disposable syringe = £15.00

Injection with antiemetic

For prescribing information on cyclizine, see section 4.6

Caution Not recommended in palliative care, see Nausea and Vomiting, p. 18

Cyclimorph® (AMCo) ^(CD2)

Cyclimorph-10® Injection, morphine tartrate 10 mg, cyclizine tartrate 50 mg/mL, net price 1-mL amp = £1.75

Dose

Moderate to severe pain (short-term use only)

- By subcutaneous, intramuscular, or intravenous injection

Child 12–18 years 1 mL, repeated not more often than every 4 hours, max. 3 doses in any 24-hour period

Cyclimorph-15® Injection, morphine tartrate 15 mg, cyclizine tartrate 50 mg/mL, net price 1-mL amp = £1.82

Dose

Moderate to severe pain (short-term use only)

- By subcutaneous, intramuscular, or intravenous injection

Child 12–18 years 1 mL, repeated not more often than every 4 hours, max. 3 doses in any 24-hour period

OXYCODONE HYDROCHLORIDE

Cautions see notes above; also toxic psychosis; pancreatitis

Contra-indications see notes above; also acute abdomen; delayed gastric emptying; chronic constipation; cor pulmonale

Hepatic impairment max. initial dose 2.5 mg every 6 hours in children not currently treated with an opioid with mild impairment; avoid in moderate to severe impairment; see also notes above

Renal impairment max. initial dose 2.5 mg every 6 hours in children not currently treated with an opioid with mild to moderate impairment; avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73m²; see also notes above

Pregnancy see notes above

Breast-feeding present in milk—avoid

Side-effects see notes above; also diarrhoea, abdominal pain, anorexia, dyspepsia; bronchospasm, dyspnoea, impaired cough reflex; asthenia, anxiety; chills; less commonly paralytic ileus, cholestasis, gastritis, flatulence, dysphagia, taste disturbance, belching, hiccups, vasodilatation, supraventricular tachycardia, syncope, amnesia, hypoaesthesia, restlessness, seizures, hypotonia, paraesthesia, disorientation, malaise, agitation, speech disorder, tremor, pyrexia, amenorrhoea, thirst, dehydration, muscle fasciculation, and dry skin

Licensed use oral solution, *Oxynorm®*, *Longtec®*, and *Oxycontin®* not licensed for use in children; capsules

and *Dolcodon*® PR not licensed for use in children under 12 years

Indications and dose

Moderate to severe pain in palliative care (see also Pain Management with Opioids, (p. 16))

• By mouth

Child 1 month–12 years initially 200 micrograms/kg (up to 5 mg) every 4–6 hours, dose increased if necessary according to severity of pain

Child 12–18 years initially 5 mg every 4–6 hours, dose increased if necessary according to severity of pain

Oxycodone (Non-proprietary)

Capsules, oxycodone hydrochloride 5 mg, net price 56 = £11.43; 10 mg, 56 = £22.86; 20 mg, 56 = £45.71. Label: 2

Oral solution, oxycodone hydrochloride 5 mg/5 mL, net price 250-mL pack = £9.71. Label: 2

Concentrated oral solution, oxycodone hydrochloride 10 mg/mL, net price 120-mL pack = £46.63. Label: 2

Oxynorm® (Napp)

Capsules, oxycodone hydrochloride 5 mg (orange/beige), net price 56-cap pack = £11.43; 10 mg (white/beige), 56-cap pack = £22.86; 20 mg (pink/beige), 56-cap pack = £45.71. Label: 2

Liquid (= oral solution), sugar-free, oxycodone hydrochloride 5 mg/5 mL, net price 250 mL = £9.71. Label: 2

Concentrate (= concentrated oral solution), sugar-free, oxycodone hydrochloride 10 mg/mL, net price 120 mL = £46.63. Label: 2

■ Modified release

Dolcodon® PR (Zentiva)

Tablets, f/c, m/r, oxycodone hydrochloride 5 mg (white), net price 28-tab pack = £12.50; 10 mg (pink), 56-tab pack = £24.99; 20 mg (white), 56-tab pack = £49.98; 40 mg (pink), 56-tab pack = £99.98. Label: 2, 25

Dose

Moderate to severe pain in palliative care

• By mouth

Child 8–12 years initially, 5 mg every 12 hours, increased if necessary according to severity of pain

Child 12–18 years initially, 10 mg every 12 hours, increased if necessary according to severity of pain

Longtec® (Qdem)

Tablets, m/r, oxycodone hydrochloride 5 mg (blue), net price 28-tab pack = £10.00; 10 mg (white), 56-tab pack = £19.99; 20 mg (pink), 56-tab pack = £39.98; 40 mg (yellow), 56-tab pack = £79.98; 80 mg (green), 56-tab pack = £159.98. Label: 2, 25

Dose

Moderate to severe pain in palliative care

• By mouth

Child 8–12 years initially, 5 mg every 12 hours, increased if necessary according to severity of pain

Child 12–18 years initially, 10 mg every 12 hours, increased if necessary according to severity of pain

OxyContin® (Napp)

Tablets, f/c, m/r, oxycodone hydrochloride 5 mg (blue), net price 28-tab pack = £12.52; 10 mg (white), 56-tab pack = £25.04; 15 mg (grey), 56-tab pack = £38.12; 20 mg (pink), 56-tab pack = £50.08; 30 mg (brown), 56-tab pack = £76.23; 40 mg (yellow), 56-tab pack = £100.19; 60 mg (red), 56-tab pack = £152.49; 80 mg (green), 56-tab pack = £200.39; 120 mg (purple), 56-tab pack = £305.02. Label: 2, 25

Dose

Moderate to severe pain in palliative care

• By mouth

Child 8–12 years initially, 5 mg every 12 hours, increased if necessary according to severity of pain

Child 12–18 years initially, 10 mg every 12 hours, increased if necessary according to severity of pain

PAPAVERETUM

Safe Practice

Do not confuse with papaverine

A mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride and 20 parts of codeine hydrochloride

To avoid confusion, the figures of 7.7 mg/mL or 15.4 mg/mL should be used for prescribing purposes

Cautions see notes above; supraventricular tachycardia

Contra-indications see notes above; heart failure secondary to chronic lung disease; phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding therapeutic doses unlikely to affect infant

Side-effects see notes above; also hypothermia

Indications and dose

Premedication, postoperative analgesia, severe chronic pain

• By subcutaneous or intramuscular injection

Neonate 115 micrograms/kg repeated every 4 hours if necessary

Child 1–12 months 154 micrograms/kg repeated every 4 hours if necessary

Child 1–6 years 1.93–3.85 mg repeated every 4 hours if necessary

Child 6–12 years 3.85–7.7 mg repeated every 4 hours if necessary

Child 12–18 years 7.7–15.4 mg repeated every 4 hours if necessary

• By intravenous injection

Generally 25–50% of the corresponding subcutaneous or intramuscular dose

Papaveretum (Non-proprietary)

Injection, papaveretum 15.4 mg/mL (providing the equivalent of 10 mg of anhydrous morphine/mL), net price 1-mL amp = £4.90

PETHIDINE HYDROCHLORIDE (Meperidine)

Cautions see notes above; not suitable for severe continuing pain; accumulation of metabolites may result in neurotoxicity; cardiac arrhythmias, severe cor pulmonale

Contra-indications see notes above; pheochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding present in milk but not known to be harmful

Side-effects see notes above; also restlessness, tremor, and hypothermia; convulsions reported in overdosage

Indications and dose

Obstetric analgesia

- By subcutaneous or by intramuscular injection

Child 12–18 years 1 mg/kg (max. 100 mg), repeated 1–3 hours later if necessary; max. 400 mg in 24 hours

Pethidine (Non-proprietary) CD2

Injection, pethidine hydrochloride 50 mg/mL, net price 1-mL amp = 47p, 2-mL amp = 45p; 10 mg/mL, 5-mL amp = £3.17, 10-mL amp = £2.18

TRAMADOL HYDROCHLORIDE

Cautions see notes above; impaired consciousness; excessive bronchial secretions; not suitable as substitute in opioid-dependent patients

General anaesthesia Not recommended for analgesia during potentially light planes of general anaesthesia (possibly increased intra-operative recall reported)

Contra-indications see notes above; uncontrolled epilepsy

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy embryotoxic in animal studies—manufacturer advises avoid; see also notes above

Breast-feeding amount probably too small to be harmful, but manufacturer advises avoid

Side-effects see notes above; also diarrhoea, retching, fatigue, paraesthesia; *less commonly* gastritis, and flatulence; *rarely* anorexia, syncope, hypertension, bronchospasm, dyspnoea, wheezing, seizures, and muscle weakness; blood disorders also reported

Indications and dose

Moderate to severe pain

- By mouth

Child 12–18 years 50–100 mg not more often than every 4 hours; total of more than 400 mg daily not usually required

- By intravenous injection (over 2–3 minutes) or by intravenous infusion or by intramuscular injection

Child 12–18 years 50–100 mg every 4–6 hours

Postoperative pain

- By intravenous injection (over 2–3 minutes)

Child 12–18 years 100 mg initially then 50 mg every 10–20 minutes if necessary up to total max. 250 mg (including initial dose) in first hour, then 50–100 mg every 4–6 hours; max. 600 mg daily

Administration for intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%

Tramadol Hydrochloride (Non-proprietary) PoM

Capsules, tramadol hydrochloride 50 mg, net price 30-cap pack = 99p, 100-cap pack = £3.30. Label: 2
Brands include *Zamadol*[®]

Oral drops, tramadol hydrochloride 100 mg/mL (2.5 mg/drop), net price 10 mL = £3.50. Label: 2, 13

Orodispersible tablets, tramadol hydrochloride 50 mg, net price 60-tab pack = £7.12. Label: 2, counselling, administration

Counselling Tramadol hydrochloride orodispersible tablets should be sucked and then swallowed. May also be dispersed in water

Brands include *Zamadol*[®]

Injection, tramadol hydrochloride 50 mg/mL, net price 2-mL amp = 91p

Brands include *Zamadol*[®]

Zydol[®] (Grünenthal) PoM

Capsules, yellow, tramadol hydrochloride 50 mg, net price 30-cap pack = £2.29, 100-cap pack = £7.63. Label: 2

Soluble tablets, tramadol hydrochloride 50 mg, net price 20-tab pack = £2.79, 100-tab pack = £13.33. Label: 2, 13

Injection, tramadol hydrochloride 50 mg/mL, net price 2-mL amp = 80p

Modified-release 12-hourly preparations

Tramadol m/r preparations (Non-proprietary) PoM

Tablets, m/r, tramadol hydrochloride 100 mg, net price 60 = £17.21; 150 mg, 60 = £27.39; 200 mg, 60 = £36.52. Label: 2, 25

Brands include *Mabron*[®], *Marol*[®], *Zeridame*[®] SR

Capsules, m/r, tramadol hydrochloride 50 mg, net price 60 = £6.56; 100 mg, 60 = £14.72; 150 mg, 60 = £22.08; 200 mg, 60 = £29.43. Label: 2, 25

Brands include *Maxitram*[®] SR, *Tramquel*[®] SR, *Zamadol*[®] SR

Dose

Moderate to severe pain

- By mouth

Child 12–18 years 50–100 mg twice daily increased if necessary to 150–200 mg twice daily; total of more than 400 mg daily not usually required

Note Some capsule preparations may be opened and the contents swallowed immediately without chewing—check individual preparations

Important Do not confuse with modified-release 24-hourly preparations

Zydol SR[®] (Grünenthal) PoM

Tablets, m/r, f/c, tramadol hydrochloride 50 mg (yellow), net price 60-tab pack = £4.60; 100 mg, 60-tab pack = £18.26; 150 mg (light orange), 60-tab pack = £27.39; 200 mg (dark orange), 60-tab pack = £36.52. Label: 2, 25

Dose

Moderate to severe pain

- By mouth

Child 12–18 years 50–100 mg twice daily increased if necessary to 150–200 mg twice daily; total of more than 400 mg daily not usually required

Modified-release 24-hourly preparations

Tramadol m/r preparations (Non-proprietary) (PoM)

Tablets, m/r, tramadol hydrochloride 100 mg, net price 30 = £14.10; 150 mg, 28 = £10.70; 200 mg, 30 = £14.98; 300 mg, 30 = £22.47; 400 mg, 28 = £28.51. Label: 2, 25

Brands include Tradorec XL[®], Zamadol[®] 24hr

Dose

Moderate to severe pain

- By mouth

Child 12–18 years initially 100–150 mg once daily, increased if necessary; usual max. 400 mg once daily

Important Do not confuse with modified-release 12-hourly preparations

Zydol XL[®] (Grünenthal) (PoM)

Tablets, m/r, f/c, tramadol hydrochloride 150 mg, net price 30-tab pack = £12.18; 200 mg, 30-tab pack = £17.98; 300 mg, 30-tab pack = £24.94; 400 mg, 30-tab pack = £32.47. Label: 2, 25

Dose

Moderate to severe pain

- By mouth

Child 12–18 years 150 mg once daily increased if necessary; more than 400 mg once daily not usually required

With paracetamol

section 4.7.1

4.7.3 Neuropathic pain

Neuropathic pain, which occurs as a result of damage to neural tissue, includes *compression neuropathies*, *peripheral neuropathies* (e.g. due to diabetes, HIV infection, chemotherapy), *trauma*, *idiopathic neuropathy*, *central pain* (e.g. pain following spinal cord injury and syringomyelia), *postherpetic neuralgia*, and *phantom limb pain*. The pain may occur in an area of sensory deficit and may be described as burning, shooting or scalding; it may be accompanied by pain that is evoked by a non-noxious stimulus (allodynia).

Children with chronic neuropathic pain require multidisciplinary management, which may include physiotherapy and psychological support. Neuropathic pain is generally managed with a tricyclic antidepressant such as **amitriptyline** (p. 185) or antiepileptic drugs such as **carbamazepine** (p. 220). Children with localised pain may benefit from **topical local anaesthetic** preparations section 15.2, particularly while awaiting specialist review. Neuropathic pain may respond only partially to **opioid analgesics**. A corticosteroid may help to relieve pressure in compression neuropathy and thereby reduce pain.

For the management of neuropathic pain in palliative care see Pain, (p. 16).

Chronic facial pain Chronic oral and facial pain including persistent idiopathic facial pain (also termed 'atypical facial pain') and temporomandibular dysfunction (previously termed temporomandibular joint pain dysfunction syndrome) may call for prolonged use of analgesics or for other drugs. Tricyclic antidepressants (section 4.3.1) may be useful for facial pain [unlicensed indication], but are not on the Dental Practitioners' List. Disorders of this type require specialist referral and psychological support to accompany drug treatment. Children on long-term therapy need to be monitored both for progress and for side-effects.

4.7.4 Antimigraine drugs

4.7.4.1 Treatment of acute migraine

4.7.4.2 Prophylaxis of migraine

4.7.4.3 Cluster headache and the trigeminal autonomic cephalalgias

4.7.4.1 Treatment of acute migraine

Treatment of a migraine attack should be guided by response to previous treatment and the severity of the attacks. A **simple analgesic** such as paracetamol (preferably in a soluble or dispersible form) or an NSAID, usually ibuprofen, is often effective; concomitant **anti-emetic** treatment may be required. If treatment with an analgesic is inadequate, an attack may be treated with a specific antimigraine compound such as the 5HT₁-receptor agonist **sumatriptan**. **Ergot alkaloids** are associated with many side-effects and should be avoided.

Excessive use of acute treatments for migraine (opioid and non-opioid analgesics, 5HT₁-receptor agonists, and ergotamine) is associated with medication-overuse headache (analgesic-induced headache); therefore, increasing consumption of these medicines needs careful management.

5HT₁-receptor agonists

5HT₁-receptor agonists are used in the treatment of acute migraine attacks; treatment of children should be initiated by a specialist. The 5HT₁-receptor agonists ('triptans') act on the 5HT (serotonin) 1B/1D receptors and they are therefore sometimes referred to as 5HT_{1B/1D}-receptor agonists. A 5HT₁-receptor agonist may be used during the established headache phase of an attack and is the preferred treatment in those who fail to respond to conventional analgesics. 5HT₁-receptor agonists are **not** indicated for the treatment of hemiplegic, basilar, or ophthalmoplegic migraine.

If a child does not respond to one 5HT₁-receptor agonist, an alternative 5HT₁-receptor agonist should be tried. For children who have prolonged attacks that frequently recur despite treatment with a 5HT₁-receptor agonist, combination therapy with an NSAID such as naproxen can be considered. **Sumatriptan** and **zolmitriptan** are used for migraine in children. They may also be of value in cluster headache (see also section 4.7.4.3).

Cautions See **interactions**: Appendix 1 (5HT₁ agonists).

SUMATRIPTAN

Cautions see under 5HT₁-receptor agonists above; pre-existing cardiac disease; history of seizures; sensitivity to sulfonamides; **interactions**: Appendix 1 (5HT₁ agonists)

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving)

Contra-indications vasospasm; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease; moderate and severe hypertension

Hepatic impairment reduce dose of oral therapy; avoid in severe impairment

Renal impairment use with caution

Pregnancy limited experience—avoid unless potential benefit outweighs risk

Breast-feeding present in milk but amount probably too small to be harmful; withhold breast-feeding for 12 hours

Side-effects nausea, vomiting; sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis), transient increase in blood pressure, flushing; dyspnoea; drowsiness, dizziness, weakness; myalgia; *also reported* diarrhoea, ischaemic colitis, hypotension, bradycardia or tachycardia, palpitation, arrhythmias, myocardial infarction, Raynaud's syndrome, anxiety, seizures, tremor, dystonia, nystagmus, arthralgia, visual disturbances, sweating; epistaxis with nasal spray

Licensed use tablets and injection not licensed for use in children; not licensed for treating cluster headache in children; intranasal dose for migraine not licensed

Indications and dose

Treatment of acute migraine

• By mouth

Child 6–10 years 25 mg as a single dose, repeated once after at least 2 hours if migraine recurs

Child 10–12 years 50 mg as a single dose, repeated once after at least 2 hours if migraine recurs

Child 12–18 years 50–100 mg as a single dose, repeated once after at least 2 hours if migraine recurs

• By subcutaneous injection (using auto-injector)

Child 10–18 years 6 mg as a single dose, repeated once after at least 1 hour if migraine recurs; max. 12 mg in 24 hours

• Intranasally

Child 12–18 years 10–20 mg as a single dose, repeated once after at least 2 hours if migraine recurs; max. 40 mg in 24 hours

Treatment of acute cluster headache (under specialist supervision)

• By subcutaneous injection (using auto-injector)

Child 10–18 years 6 mg as a single dose, repeated once after at least 1 hour if headache recurs; max. 12 mg in 24 hours

• Intranasally

Child 12–18 years 10–20 mg as a single dose, repeated once after at least 2 hours if headache recurs; max. 40 mg in 24 hours

Note Child not responding to initial dose should not take second dose for same attack

Imigran® (GSK) (PoM)

Tablets, sumatriptan (as succinate) 50 mg, net price 6-tab pack = £26.54; 100 mg, 6-tab pack = £42.90.

Label: 3, 10, patient information leaflet

Injection, sumatriptan (as succinate) 12 mg/mL (= 6 mg/0.5-mL syringe), net price, treatment pack (2 × 0.5-mL prefilled syringes and auto-injector) = £42.47; refill pack 2 × 0.5-mL prefilled cartridges = £40.41. Label: 3, 10, patient information leaflet

Nasal spray, sumatriptan 10 mg/0.1-mL actuation, net price 2 unit-dose spray device = £11.80; 20 mg/0.1-mL actuation, 2 unit-dose spray device = £11.80, 6 unit-dose spray device = £35.39. Label: 3, 10, patient information leaflet

Imigran Radis® (GSK) (PoM)

Tablets, f/c, sumatriptan (as succinate) 50 mg (pink), net price 6-tab pack = £23.90; 100 mg (white), 6-tab pack = £42.90. Label: 3, 10, patient information leaflet

ZOLMITRIPTAN

Cautions see under 5HT₁-receptor agonists above; should not be taken within 24 hours of any other 5HT₁-receptor agonist; **interactions**: Appendix 1 (5HT₁ agonists)

Contra-indications vasospasm; Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways; previous cerebrovascular accident or transient ischaemic attack; ischaemic heart disease; uncontrolled hypertension

Hepatic impairment max. 5 mg in 24 hours in moderate or severe impairment

Pregnancy limited experience—avoid unless potential benefit outweighs risk

Breast-feeding use with caution—present in milk in animal studies

Side-effects abdominal pain, dry mouth, nausea, vomiting, palpitation, sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis), dysphagia, dizziness, drowsiness, headache, paraesthesia, asthenia, myalgia, muscle weakness; *less commonly* tachycardia, transient increase in blood pressure, polyuria; *rarely* urticaria; *very rarely* gastro-intestinal and splenic infarction, ischaemic colitis, angina pectoris, myocardial infarction; *with nasal spray*, taste disturbance, and epistaxis

Licensed use not licensed for use in children

Indications and dose

Treatment of acute migraine

• By mouth

Child 12–18 years 2.5 mg, repeated after not less than 2 hours if migraine recurs (if response unsatisfactory after 3 attacks consider increasing dose to 5 mg or switching to alternative treatment); max. 10 mg in 24 hours

• Intranasally

Child 12–18 years 5 mg (1 spray) into 1 nostril, repeated after not less than 2 hours if migraine recurs; max. 10 mg in 24 hours

¹Sumatriptan (Non-proprietary) (PoM)

Tablets, sumatriptan (as succinate) 50 mg, net price 6-tab pack = £1.41; 100 mg, 6-tab pack = £1.78. Label: 3, 10, patient information leaflet

1. Sumatriptan 50 mg tablets can be sold to the public to treat previously diagnosed migraine; max. daily dose 100 mg

Treatment of acute cluster headache

- **Intranasally**

Child 12–18 years 5 mg (1 spray) into 1 nostril, repeated after not less than 2 hours if headache recurs; max. 10 mg in 24 hours

Zolmitriptan (Non-proprietary) (PoM)

Tablets, zolmitriptan 2.5 mg, net price 6-tab pack = £1.21

Orodispersible tablets, zolmitriptan 2.5 mg, net price 6-tab pack = £1.33; 5 mg, 6-tab pack = £12.48. Counselling, administration

Counselling Zolmitriptan orodispersible tablets should be placed on the tongue, allowed to disperse and swallowed

Zomig® (AstraZeneca) (PoM)

Tablets, f/c, yellow, zolmitriptan 2.5 mg, net price 6-tab pack = £23.94

Orodispersible tablets (*Zomig Rapimelt*®), zolmitriptan 2.5 mg, net price 6-tab pack = £23.99; 5 mg, 6-tab pack = £23.94. Counselling, administration

Counselling *Zomig Rapimelt*® should be placed on the tongue, allowed to disperse and swallowed

Excipients include aspartame equivalent to phenylalanine 2.81 mg/tablet (section 9.4.1)

Nasal spray, zolmitriptan 5 mg/0.1-mL unit-dose spray device, net price 6 unit-dose sprays = £36.50

Antiemetics

Antiemetics (section 4.6), including domperidone, phenothiazines, and antihistamines, relieve the nausea associated with migraine attacks. Antiemetics may be given by intramuscular injection or rectally if vomiting is a problem. Domperidone has the added advantage of promoting gastric emptying and normal peristalsis; a single dose should be given at the onset of symptoms (**important:** for MHRA advice on the use of domperidone, see p. 193)

4.7.4.2 Prophylaxis of migraine

Where migraine attacks are frequent, possible provoking factors such as stress should be sought; combined oral contraceptives may also provoke migraine. Preventive treatment should be considered if migraine attacks interfere with school and social life, particularly for children who:

- suffer at least two attacks a month;
- suffer an increasing frequency of headaches;
- suffer significant disability despite suitable treatment for migraine attacks;
- cannot take suitable treatment for migraine attacks.

In children it is often possible to stop prophylaxis after a period of treatment.

Propranolol (section 2.4) may be effective in preventing migraine in children but it is contra-indicated in those with asthma. Side-effects such as depression and postural hypotension can further limit its use.

Pizotifen, an antihistamine and serotonin antagonist, may also be used but its efficacy in children has not been clearly established. Common side-effects include drowsiness and weight gain.

Topiramate (section 4.8.1) is licensed for migraine prophylaxis.

PIZOTIFEN

Cautions urinary retention; susceptibility to angle-closure glaucoma; history of epilepsy; avoid abrupt withdrawal; **interactions:** Appendix 1 (pizotifen)

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Hepatic impairment use with caution

Renal impairment use with caution

Pregnancy avoid unless potential benefit outweighs risk

Breast-feeding amount probably too small to be harmful, but manufacturer advises avoid

Side-effects dry mouth, nausea, dizziness, drowsiness, increased appetite, weight gain; *less commonly* constipation; *rarely* anxiety, aggression, insomnia, paraesthesia, hallucination, depression, arthralgia, myalgia; *very rarely* seizures; jaundice, hepatitis, and muscle cramps also reported

Licensed use 1.5-mg tablets not licensed for use in children

Indications and dose**Prophylaxis of migraine**

- **By mouth**

Child 5–18 years initially 500 micrograms at night increased gradually up to 1.5 mg daily in divided doses; max. single dose (at night) 1 mg

Pizotifen (Non-proprietary) (PoM)

Tablets, pizotifen (as hydrogen malate), 500 micrograms, net price 28-tab pack = £1.12; 1.5 mg, 28-tab pack = £1.61. Label: 2

Sanomigran® (Novartis) (PoM)

Tablets, both ivory-yellow, s/c, pizotifen (as hydrogen malate), 500 micrograms, net price 60-tab pack = £2.06; 1.5 mg, 28-tab pack = £3.42. Label: 2

4.7.4.3 Cluster headache and the trigeminal autonomic cephalalgias

Cluster headache rarely responds to standard analgesics. **Sumatriptan** given by subcutaneous injection is the drug of choice for the treatment of cluster headache. If an injection is unsuitable, sumatriptan nasal spray or zolmitriptan nasal spray may be used. Treatment should be initiated by a specialist. Alternatively, 100% oxygen at a rate of 10–15 litres/minute for 10–20 minutes is useful in aborting an attack.

The other trigeminal autonomic cephalalgias, paroxysmal hemicrania (sensitive to indometacin), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, are seen rarely and are best managed by a specialist.

4.8 Antiepileptics

- 4.8.1 Control of the epilepsies
- 4.8.2 Drugs used in status epilepticus
- 4.8.3 Febrile convulsions

4.8.1 Control of the epilepsies

The object of treatment is to prevent the occurrence of seizures by maintaining an effective dose of one or more antiepileptic drugs. Careful adjustment of doses is necessary, starting with low doses and increasing gradually until seizures are controlled or there are significant adverse effects.

When choosing an antiepileptic drug, the presenting epilepsy syndrome should first be considered. If the syndrome is not clear, the seizure type should determine the choice of treatment. Concomitant medication, co-morbidity, age, sex, and the wishes of the child and carers should also be taken into account. For women of child-bearing age, see Pregnancy, p. 218 and Breast-feeding, p. 218.

The frequency of administration is often determined by the plasma-drug half-life, and should be kept as low as possible to encourage better adherence. Most antiepileptics, when used in usual dosage, can be given twice daily. Lamotrigine, perampanel, phenobarbital and phenytoin, which have long half-lives, can be given as a daily dose at bedtime. However, with large doses, some antiepileptics may need to be given 3 times daily to avoid adverse effects associated with high peak plasma-drug concentrations. Young children metabolise some antiepileptics more rapidly than adults and therefore may require more frequent doses and a higher amount per kilogram body-weight.

Management When monotherapy with a first-line antiepileptic drug has failed, monotherapy with a second drug should be tried; the diagnosis should be checked before starting an alternative drug if the first drug showed lack of efficacy. The change from one antiepileptic drug to another should be cautious, slowly withdrawing the first drug only when the new regimen has been established. Combination therapy with two or more antiepileptic drugs may be necessary, but the concurrent use of antiepileptic drugs increases the risk of adverse effects and drug interactions (see below). If combination therapy does not bring about worthwhile benefits, revert to the regimen (monotherapy or combination therapy) that provided the best balance between tolerability and efficacy. A single antiepileptic drug should be prescribed wherever possible and will achieve seizure control for the majority of children.

MHRA/CHM advice

Antiepileptic drugs: new advice on switching between different manufacturers' products for a particular drug (November 2013)

The CHM has reviewed spontaneous adverse reactions received by the MHRA and publications that reported potential harm arising from switching of antiepileptic drugs in patients previously stabilised on a branded product to a generic. The CHM concluded that reports of loss of seizure control and/or worsening of side-effects around the time of switching between products could be explained as chance associations, but that a causal role of switching could not be ruled out in all cases. The following guidance has been issued to help minimise risk:

- Different antiepileptic drugs vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers' products of a particular drug may cause adverse effects or loss of seizure control;
- Antiepileptic drugs have been divided into three risk-based categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product. These categories are listed below;
- If it is felt desirable for a patient to be maintained on a specific manufacturer's product this should be prescribed either by specifying a brand name, or by using the generic drug name and name of the manufacturer (otherwise known as the Marketing Authorisation Holder);
- This advice relates only to antiepileptic drug use for treatment of epilepsy; it does not apply to their use in other indications (e.g. mood stabilisation, neuropathic pain);
- Please report on a Yellow Card any suspected adverse reactions to antiepileptic drugs (see Yellow Card Scheme, p. 11);
- Dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that antiepileptic drug. Such cases should be discussed and agreed with both the prescriber and patient (or carer);
- Usual dispensing practice can be followed when a specific product is not stated.

Category 1

Phenytoin, carbamazepine, phenobarbital, primidone. For these drugs, doctors are advised to ensure that their patient is maintained on a specific manufacturer's product

Category 2

Valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate. For these drugs, the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient and/or carer taking into account factors such as seizure frequency and treatment history

Category 3

Levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin. For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific concerns such as patient anxiety, and risk of confusion or dosing errors

Interactions Interactions between antiepileptics are complex and may increase toxicity without a corresponding increase in antiepileptic effect. Interactions are usually caused by hepatic enzyme induction or inhibition; displacement from protein binding sites is not usually a problem. These interactions are highly variable and unpredictable.

For interactions of antiepileptic drugs, see **Appendix 1**; for advice on hormonal contraception and enzyme-inducing drugs, see section 7.3.1 and section 7.3.2.

Significant interactions that occur **between antiepileptics** and that may affect dosing requirements are as follows:

Note

Check under each drug for possible interactions when two or more antiepileptic drugs are used

Carbamazepine

often lowers plasma concentration of clobazam, clonazepam, lamotrigine, perampanel, phenytoin (but may also raise plasma-phenytoin concentration), tiagabine, topiramate, valproate, and an active metabolite of oxcarbazepine

sometimes lowers plasma concentration of ethosuximide, primidone (but tendency for corresponding increase in plasma-phenobarbital concentration), and rufinamide

sometimes raises plasma concentration of phenobarbital and primidone-derived phenobarbital

Ethosuximide

sometimes raises plasma concentration of phenytoin

Lamotrigine

sometimes raises plasma concentration of an active metabolite of carbamazepine (but evidence is conflicting)

Oxcarbazepine

often lowers plasma concentration of perampanel

sometimes lowers plasma concentration of carbamazepine (but may raise plasma concentration of an active metabolite of carbamazepine)

sometimes raises plasma concentration of phenytoin

often raises plasma concentration of phenobarbital and primidone-derived phenobarbital

Phenobarbital or Primidone

often lowers plasma concentration of clonazepam, lamotrigine, phenytoin (but may also raise plasma-phenytoin concentration), tiagabine, valproate, and an active metabolite of oxcarbazepine

sometimes lowers plasma concentration of ethosuximide, rufinamide, and topiramate

Phenytoin

often lowers plasma concentration of clonazepam, carbamazepine, lamotrigine, perampanel, tiagabine, topiramate, valproate, and an active metabolite of oxcarbazepine

often raises plasma concentration of phenobarbital and primidone-derived phenobarbital

sometimes lowers plasma concentration of ethosuximide, primidone (by increasing conversion to phenobarbital), and rufinamide

Rufinamide

sometimes lowers plasma concentration of carbamazepine

sometimes raises plasma concentration of phenytoin

Stiripentol

often raises plasma concentration of carbamazepine, clobazam, phenobarbital, primidone-derived phenobarbital, and phenytoin

Topiramate

often lowers plasma concentration of perampanel

sometimes raises plasma concentration of phenytoin

Valproate

sometimes lowers plasma concentration of an active metabolite of oxcarbazepine

often raises plasma concentration of lamotrigine, phenobarbital, primidone-derived phenobarbital, phenytoin (but may also lower), and an active metabolite of carbamazepine

sometimes raises plasma concentration of ethosuximide and rufinamide

Vigabatrin

often lowers plasma concentration of phenytoin

Withdrawal Antiepileptics should be withdrawn under specialist supervision. Avoid abrupt withdrawal, particularly of barbiturates and benzodiazepines because this can precipitate severe rebound seizures. Reduction in dosage should be gradual and, in the case of barbiturates, the withdrawal process may take months.

The decision to withdraw antiepileptics from a seizure-free child, and its timing, depends on individual circumstances such as the type of epilepsy and its cause. Even in children who have been seizure-free for several years, there is a significant risk of seizure recurrence on drug withdrawal.

Drugs should be gradually withdrawn over at least 2–3 months by reducing the daily dose by 10–25% at intervals of 1–2 weeks. Benzodiazepines may need to be withdrawn over 6 months or longer.

In children receiving several antiepileptic drugs, only one drug should be withdrawn at a time.

Monitoring Routine measurement of plasma concentrations of antiepileptic drugs is not usually justified, because the target concentration ranges are arbitrary and often vary between individuals. However, plasma-drug concentrations may be measured in children with worsening seizures, status epilepticus, suspected non-compliance, or suspected toxicity. Similarly, haematological and biochemical monitoring should not be undertaken unless clinically indicated.

Plasma concentration of some medications may change during pregnancy and monitoring may be required (see under Pregnancy, below).

Antiepileptic hypersensitivity syndrome Antiepileptic hypersensitivity syndrome is a rare but potentially fatal syndrome associated with some antiepileptic drugs (carbamazepine, lacosamide, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide); rarely cross-sensitivity occurs between some of these antiepileptic drugs. Some other antiepileptic drugs (eslicarbazepine, stiripentol,

and **zonisamide**) have a theoretical risk. The symptoms usually start between 1 and 8 weeks of exposure; fever, rash, and lymphadenopathy are most commonly seen. Other systemic signs include liver dysfunction, haematological, renal, and pulmonary abnormalities, vasculitis, and multi-organ failure. If signs or symptoms of hypersensitivity syndrome occur, the drug should be withdrawn immediately, the child should not be re-exposed, and expert advice should be sought.

Driving Older children with epilepsy may drive a motor vehicle (but not a large goods or passenger carrying vehicle) provided that they have been seizure-free for one year or, if subject to attacks only while asleep, have established a 3-year period of asleep attacks without awake attacks. Those affected by drowsiness should not drive or operate machinery.

Guidance issued by the Drivers Medical Unit of the Driver and Vehicle Licensing Agency (DVLA) recommends that patients should be advised not to drive during medication changes or withdrawal of antiepileptic drugs, and for 6 months afterwards.

Patients who have had a first or single epileptic seizure must not drive for 6 months (5 years in the case of large goods or passenger carrying vehicles) after the event; driving may then be resumed, provided the patient has been assessed by a specialist as fit to drive because no abnormality was detected on investigation.

Pregnancy Young women of child-bearing potential should discuss with a specialist the impact of both epilepsy, and its treatment, on the outcome of pregnancy.

There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially if used during the first trimester and particularly if the patient takes two or more antiepileptic drugs). Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and long-term neurodevelopmental effects. Valproate should not be used during pregnancy or in women of child-bearing potential unless there is no safer alternative and only after a careful discussion of the risks. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses or as modified-release tablets to avoid peaks in plasma-valproate concentrations; doses greater than 1 g daily are associated with an increased risk of teratogenicity. Specialist prenatal monitoring should be instigated when valproate has been taken in pregnancy. There is also an increased risk of teratogenicity with phenytoin, primidone, phenobarbital, lamotrigine, and carbamazepine. Topiramate carries an increased risk of cleft palate if taken in the first trimester of pregnancy. There is not enough evidence to establish the risk of teratogenicity with other antiepileptic drugs.

Prescribers should also consider carefully the choice of antiepileptic therapy in pre-pubescent girls who may later become pregnant.

Young women of child-bearing potential who take antiepileptic drugs should be given contraceptive advice. Some antiepileptic drugs can reduce the efficacy of hormonal contraceptives, and the efficacy of some antiepileptics may be affected by hormonal contraceptives (see section 7.3.1 and interactions of antiepileptics, Appendix 1).

Young women who want to become pregnant should be referred to a specialist for advice in advance of concep-

tion. For some women, the severity of seizure or the seizure type may not pose a serious threat, and drug withdrawal may be considered; therapy may be resumed after the first trimester. If treatment with antiepileptic drugs must continue throughout pregnancy, then monotherapy is preferable at the lowest effective dose.

Once an unplanned pregnancy is discovered it is usually too late for changes to be made to the treatment regimen; the risk of harm to the mother and fetus from convulsive seizures outweighs the risk of continued therapy. The likelihood of a young woman who is taking antiepileptic drugs having a baby with no malformations is at least 90%, and it is important that women do not stop taking essential treatment because of concern over harm to the fetus.

To reduce the risk of neural tube defects, folate supplementation (section 9.1.2) is advised before conception and throughout the first trimester.

The concentration of antiepileptic drugs in the plasma can change during pregnancy. Doses of phenytoin p. 228, carbamazepine, and lamotrigine should be adjusted on the basis of plasma-drug concentration monitoring; the dose of other antiepileptic drugs should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. Plasma-drug concentration monitoring during pregnancy is also useful to check compliance. Additionally, in patients taking topiramate or levetiracetam, it is recommended that fetal growth is monitored.

Young women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol, see section 4.8.2.

Routine injection of vitamin K (section 9.6.6) at birth minimises the risk of neonatal haemorrhage associated with antiepileptics.

Withdrawal effects in the newborn may occur with some antiepileptic drugs, in particular benzodiazepines and phenobarbital, and can take several days to diminish.

Epilepsy and Pregnancy Register

All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register (Tel: 0800 389 1248).

Breast-feeding Young women taking antiepileptic monotherapy should generally be encouraged to breast-feed; if a young woman is on combination therapy or if there are other risk factors, such as premature birth, specialist advice should be sought.

All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones. Infants should also be monitored for adverse effects associated with the antiepileptic drug particularly with newer antiepileptics, if the antiepileptic is readily transferred into breast-milk causing high infant serum-drug concentrations (e.g. ethosuximide, lamotrigine, and primidone), or if slower metabolism in the infant causes drugs to accumulate (e.g. phenobarbital and lamotrigine). Serum-drug concentration monitoring should be undertaken in breast-fed infants if suspected adverse reactions develop; if toxicity develops it may

be necessary to introduce formula feeds to limit the infant's drug exposure, or to wean the infant off breast-milk altogether.

Primidone, phenobarbital, and the benzodiazepines are associated with an established risk of drowsiness in breast-fed babies and caution is required.

Withdrawal effects may occur in infants if a mother suddenly stops breast-feeding, particularly if she is taking phenobarbital, primidone, or lamotrigine.

Focal seizures with or without secondary generalisation

Carbamazepine and lamotrigine are the drugs of choice for focal seizures; **levetiracetam**, **oxcarbazepine** and **sodium valproate** can be considered if these are unsuitable. These drugs may also be used as adjunctive treatment. Other adjunctive options include **clobazam**, **gabapentin**, and **topiramate**. If adjunctive treatment is ineffective or not tolerated, a tertiary specialist should be consulted who may consider **eslicarbazepine**, **lacosamide**, **phenobarbital**, **phenytoin**, **pregabalin**, **tiagabine**, **vigabatrin**, and **zonisamide**.

Generalised seizures

Tonic-clonic seizures The drug of choice for newly diagnosed tonic-clonic seizures in children is **sodium valproate**, or **lamotrigine** where sodium valproate is unsuitable (but may exacerbate myoclonic seizures). In children with established epilepsy with generalised tonic-clonic seizures only, lamotrigine may be prescribed as the first-line choice. **Carbamazepine** or **oxcarbazepine** can also be considered but may exacerbate myoclonic or absence seizures. **Clobazam**, **lamotrigine**, **levetiracetam**, **sodium valproate**, or **topiramate** may be used as adjunctive treatment if monotherapy is ineffective or not tolerated.

Absence seizures **Ethosuximide** and **sodium valproate** are the drugs of choice for absence seizures and syndromes; lamotrigine can be used if these are unsuitable, ineffective or not tolerated. Sodium valproate should be used as the first choice if there is a high risk of generalised tonic-clonic seizures. A combination of any two of these drugs may be used if monotherapy is ineffective. Second-line therapy includes **clobazam**, **clonazepam**, **levetiracetam**, **topiramate** or **zonisamide** which may be considered by a tertiary specialist if adjunctive treatment fails. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin are not recommended in absence seizures or syndromes.

Myoclonic seizures Myoclonic seizures (myoclonic jerks) occur in a variety of syndromes, and response to treatment varies considerably. Sodium valproate is the drug of choice; consider levetiracetam or topiramate if sodium valproate is unsuitable (but consider the less favourable side-effect profile of topiramate). A combination of any two of these drugs may be used if monotherapy is ineffective or poorly tolerated. Second-line therapy includes **clobazam**, **clonazepam**, **piracetam** or **zonisamide** which should be prescribed under the supervision of a tertiary specialist. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin are not recommended for the treatment of myoclonic seizures.

Tonic and atonic seizures Tonic or atonic seizures are treated with sodium valproate; lamotrigine can be considered as adjunctive treatment if sodium valproate is ineffective or not tolerated. If adjunctive treatment fails, a tertiary specialist should be consulted who may consider **rufinamide** or **topiramate**. Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin are not recommended in atonic or tonic seizures.

Epilepsy syndromes

Infantile spasms Vigabatrin is the drug of choice for infantile spasms associated with tuberous sclerosis. Corticosteroids, such as **prednisolone** (section 6.3.2) or **tetracosactide** (section 6.5.1), are second-line options if vigabatrin is ineffective. In spasms of other causes, vigabatrin, prednisolone or tetracosactide can be considered as first-line options. A tertiary specialist should be consulted before treating infantile spasms.

Dravet syndrome Sodium valproate or topiramate is the treatment of choice in Dravet syndrome. **Clobazam** or **stiripentol** may be considered as adjunctive treatment. Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin should not be used as they may exacerbate myoclonic seizures. A tertiary specialist should be involved in decisions regarding treatment of Dravet syndrome.

Lennox-Gastaut syndrome Sodium valproate is the first-line drug for treating Lennox-Gastaut syndrome; lamotrigine can be used as adjunctive treatment if sodium valproate is ineffective or not tolerated. **Rufinamide** and topiramate may be considered by tertiary epilepsy specialists. Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin should not be used. Felbamate [unlicensed] may be used in tertiary specialist centres when all other treatment options have failed.

Landau-Kleffner syndrome Always discuss with or refer to tertiary epilepsy specialists.

Neonatal seizures Seizures can occur before delivery, but they are most common up to 24 hours after birth. Seizures in neonates occur as a result of biochemical disturbances, inborn errors of metabolism, hypoxic ischaemic encephalopathy, drug withdrawal, meningitis, stroke, cerebral haemorrhage or malformation, or severe jaundice (kernicterus).

Seizures caused by biochemical imbalance and those in neonates with inherited abnormal pyridoxine or biotin metabolism should be corrected by treating the underlying cause (section 9.6.2). Seizures caused by drug withdrawal following intra-uterine exposure are treated with a drug withdrawal regimen.

Phenobarbital can be used to manage neonatal seizures where there is a risk of recurrence; **phenytoin** is an alternative. **Midazolam** (p. 238) and **rectal paraldehyde** (p. 238) may also be useful in the management of acute neonatal seizures. **Lidocaine** (p. 85) may be used if other treatments are unsuccessful; lidocaine should not be given to neonates who have received phenytoin infusion because of the risk of cardiac toxicity.

Carbamazepine and oxcarbazepine

Carbamazepine is a drug of choice for focal seizures and a first-line treatment option for generalised tonic-clonic seizures. It can also be used as adjunctive treatment for focal seizures when monotherapy has been ineffective. It is essential to initiate carbamazepine therapy at a low dose and build this up slowly in small increments every 3–7 days. Some side-effects (such as headache, ataxia, drowsiness, nausea, vomiting, blurring of vision, dizziness, unsteadiness, and allergic skin reactions) are dose-related, and may be dose-limiting. These side-effects are more common at the start of treatment. Children should be offered a modified-release preparation to reduce the risk of side-effects; altering the timing of medication may also be beneficial. Carbamazepine may exacerbate tonic, atonic, myoclonic and absence seizures and is therefore not recommended if these seizures are present.

Oxcarbazepine is licensed as monotherapy or adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures. It can also be considered for the treatment of primary generalised tonic-clonic seizures [unlicensed]. Oxcarbazepine is not recommended in tonic, atonic, absence or myoclonic seizures due to the risk of seizure exacerbation.

CARBAMAZEPINE

Cautions cardiac disease (see also Contra-indications); skin reactions (see also Blood, Hepatic, or Skin disorders, below and under Side-effects); test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in the presence of HLA-B*1502 allele); history of haematological reactions to other drugs; manufacturer recommends blood counts and hepatic and renal function tests (but evidence of practical value uncertain); may exacerbate absence and myoclonic seizures; consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium; susceptibility to angle-closure glaucoma; cross-sensitivity reported with oxcarbazepine, and with phenytoin (see also Anti-epileptic Hypersensitivity Syndrome, p. 217); avoid abrupt withdrawal; **interactions:** see p. 217 and Appendix 1 (carbamazepine).

Blood, hepatic, or skin disorders Children or their carers should be told how to recognise signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. Carbamazepine should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative).

Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer's product (see also MHRA/CHM advice, p. 216).

Contra-indications AV conduction abnormalities (unless paced); history of bone-marrow depression, acute porphyria (section 9.8.2).

Hepatic impairment metabolism impaired in advanced liver disease; see also Blood, Hepatic, or Skin Disorders, above.

Renal impairment use with caution.

Pregnancy see Pregnancy, p. 218; monitor plasma-carbamazepine concentration.

Breast-feeding amount probably too small to be harmful but monitor infant for possible adverse reactions; see also Breast-feeding, p. 218.

Side-effects see notes above; also dry mouth, nausea, vomiting, oedema, ataxia, dizziness, drowsiness, fatigue, headache, hyponatraemia (leading in rare cases to water intoxication), blood disorders (including eosinophilia, leucopenia, thrombocytopenia, haemolytic anaemia, and aplastic anaemia), dermatitis, urticaria; *less commonly* diarrhoea, constipation, involuntary movements (including nystagmus), visual disturbances; *rarely* abdominal pain, anorexia, hepatitis, jaundice, vanishing bile duct syndrome, cardiac conduction disorders, hypertension, hypotension, peripheral neuropathy, dysarthria, aggression, agitation, confusion, depression, hallucinations, restlessness, paraesthesia, lymph node enlargement, muscle weakness, systemic lupus erythematosus, delayed multi-organ hypersensitivity disorder (see also Anti-epileptic Hypersensitivity Syndrome, p. 217); *very rarely* pancreatitis, stomatitis, hepatic failure, taste disturbance, exacerbation of coronary artery disease, AV block with syncope, circulatory collapse, hypercholesterolaemia, thrombophlebitis, thromboembolism, pulmonary hypersensitivity (with dyspnoea, pneumonitis, or pneumonia), psychosis, neuroleptic malignant syndrome, osteomalacia (see Cautions), osteoporosis, galactorrhoea, gynaecomastia, impaired male fertility, interstitial nephritis, renal failure, sexual dysfunction, urinary frequency, urinary retention, arthralgia, muscle pain, muscle spasm, conjunctivitis, angle-closure glaucoma, hearing disorders, acne, alterations in skin pigmentation, alopecia, hirsutism, sweating, photosensitivity, purpura, Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis; suicidal ideation.

Pharmacokinetics plasma concentration for optimum response 4–12 mg/litre (20–50 micromol/litre) measured after 1–2 weeks.

Licensed use *suppositories* not licensed for use in trigeminal neuralgia or prophylaxis of bipolar disorder.

Indications and dose

Focal and generalised tonic-clonic seizures, trigeminal neuralgia, prophylaxis of bipolar disorder

• By mouth

Child 1 month–12 years initially 5 mg/kg at night or 2.5 mg/kg twice daily, increased as necessary by 2.5–5 mg/kg every 3–7 days; usual maintenance dose 5 mg/kg 2–3 times daily; doses up to 20 mg/kg daily have been used.

Child 12–18 years initially 100–200 mg 1–2 times daily, increased slowly to usual maintenance dose 200–400 mg 2–3 times daily; in some cases doses up to 1.8 g daily may be needed.

Epilepsy for short-term use (max. 7 days) when oral therapy temporarily not possible.

• By rectum

Child 1 month–18 years use approx. 25% more than the oral dose (max. 250 mg) up to 4 times daily.

Note Suppositories of 125 mg may be considered to be approximately equivalent in therapeutic effect to tablets of 100 mg but final adjustment should always depend on clinical response (plasma concentration monitoring recommended).

Administration Oral liquid has been used rectally—should be retained for at least 2 hours (but may have laxative effect)

Carbamazepine (Non-proprietary) **[PoM]**

Tablets, scored, carbamazepine 100 mg, net price 28 = £6.27; 200 mg, 28 = £5.01; 400 mg, 28 = £2.51. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Note Patients being treated for epilepsy should be maintained on a specific manufacturer's branded or generic oral carbamazepine product. See also MHRA/CHM advice, p. 216

Dental prescribing on NHS Carbamazepine Tablets may be prescribed

Tegretol® (Novartis) **[PoM]**

Tablets, scored, carbamazepine 100 mg, net price 84-tab pack = £2.07; 200 mg, 84-tab pack = £3.83; 400 mg, 56-tab pack = £5.02. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Chewtabs, orange, carbamazepine 100 mg, net price 56-tab pack = £3.16; 200 mg, 56-tab pack = £5.88. Label: 3, 8, 21, 24, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Liquid, sugar-free, carbamazepine 100 mg/5 mL. Net price 300-mL pack = £6.12. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Suppositories, carbamazepine 125 mg, net price 5 = £8.03; 250 mg, 5 = £10.71. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Note Patients being treated for epilepsy should be maintained on a specific manufacturer's branded or generic oral carbamazepine product. See also MHRA/CHM advice, p. 216

Modified release

Carbagen® SR (Generics) **[PoM]**

Tablets, m/r, f/c, scored, carbamazepine 200 mg, net price 56-tab pack = £4.16; 400 mg, 56-tab pack = £8.20. Label: 3, 8, 25, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Note Patients being treated for epilepsy should be maintained on a specific manufacturer's branded or generic oral carbamazepine product. See also MHRA/CHM advice, p. 216

Dose

Child 5–18 years as above; total daily dose given in 1–2 divided doses

Tegretol® Prolonged Release (Novartis) **[PoM]**

Tablets, m/r, scored, carbamazepine 200 mg (beige-orange), net price 56-tab pack = £5.20; 400 mg (brown-orange), 56-tab pack = £10.24. Label: 3, 8, 25, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Note Patients being treated for epilepsy should be maintained on a specific manufacturer's branded or generic oral carbamazepine product. See also MHRA/CHM advice, p. 216

Dose

Child 5–18 years as above; total daily dose given in 2 divided doses

Administration Tegretol® Prolonged Release tablets can be halved but should not be chewed

OXCARBAZEPINE

Cautions hypersensitivity to carbamazepine (see also Antiepileptic Hypersensitivity Syndrome, p. 217); avoid abrupt withdrawal; hyponatraemia (monitor plasma-sodium concentration in patients at risk), heart failure (monitor body-weight), cardiac conduction disorders; test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele); avoid in acute porphyria (section 9.8.2); **interactions**: see p. 217 and Appendix 1 (oxcarbazepine)

Blood, hepatic, or skin disorders Children or their carers should be told how to recognise signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as lethargy, confusion, muscular twitching, fever, rash, blistering, mouth ulcers, bruising, or bleeding develop

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history (see also MHRA/CHM advice, p. 216)

Hepatic impairment caution in severe impairment—no information available

Renal impairment halve initial dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m², increase according to response at intervals of at least 1 week

Pregnancy see Pregnancy, p. 218

Breast-feeding amount probably too small to be harmful but manufacturer advises avoid; see also Breast-feeding, p. 218

Side-effects nausea, vomiting, constipation, diarrhoea, abdominal pain, dizziness, headache, drowsiness, agitation, amnesia, asthenia, ataxia, confusion, impaired concentration, depression, tremor, hyponatraemia, acne, alopecia, rash, nystagmus, visual disorders including diplopia; *less commonly* leucopenia, urticaria; *very rarely* arrhythmias, atrioventricular block, thrombocytopenia, hepatitis, pancreatitis, multi-organ hypersensitivity disorders (see also Antiepileptic Hypersensitivity Syndrome, p. 217), systemic lupus erythematosus, Stevens-Johnson syndrome, toxic epidermal necrolysis; *also reported* hypertension, suicidal ideation, hypothyroidism, bone marrow depression, aplastic anaemia, neutropenia, pancytopenia, osteoporotic bone disorders

Indications and dose

Monotherapy and adjunctive therapy of focal seizures with or without secondary generalised tonic-clonic seizures

• By mouth

Child 6–18 years initially 4–5 mg/kg (max. 300 mg) twice daily, increased according to response in steps of up to 5 mg/kg twice daily at weekly intervals (usual maintenance dose for adjunctive therapy 15 mg/kg twice daily); max. 23 mg/kg twice daily

Note In adjunctive therapy the dose of concomitant antiepileptics may need to be reduced when using high doses of oxcarbazepine

Oxcarbazepine (Non-proprietary) (PoM)

Tablets, oxcarbazepine 150 mg, net price 50-tab pack = £15.02; 300 mg, 50-tab pack = £24.47; 600 mg, 50-tab pack = £45.47. Label: 3, 8, counselling, blood, hepatic or skin disorders (see above), driving (see notes above)

Note Patients may need to be maintained on a specific manufacturer's branded or generic oxcarbazepine product, see MHRA/CHM advice, p. 216

Trileptal® (Novartis) (PoM)

Tablets, f/c, scored, oxcarbazepine 150 mg (green), net price 50-tab pack = £10.20; 300 mg (yellow), 50-tab pack = £20.40; 600 mg (pink), 50-tab pack = £40.80. Label: 3, 8, counselling, blood, hepatic or skin disorders (see above), driving (see notes above)

Oral suspension, sugar-free, oxcarbazepine 300 mg/5 mL, net price 250 mL (with oral syringe) = £40.80. Label: 3, 8, counselling, blood, hepatic or skin disorders (see above), driving (see notes above)

Excipients include propylene glycol (see Excipients, p. 2)

Note Patients may need to be maintained on a specific manufacturer's branded or generic oxcarbazepine product, see MHRA/CHM advice, p. 216

Ethosuximide

Ethosuximide is a first-line treatment option for absence seizures, and may be used as adjunctive treatment when monotherapy has failed.

ETHOSUXIMIDE

Cautions avoid abrupt withdrawal; avoid in acute porphyria (section 9.8.2); **interactions**: see p. 217 and Appendix 1 (ethosuximide)

Blood disorders Children or their carers should be told how to recognise signs of blood disorders, and advised to seek immediate medical attention if symptoms such as fever, mouth ulcers, bruising, or bleeding develop

Hepatic impairment use with caution

Renal impairment use with caution

Pregnancy see Pregnancy, p. 218

Breast-feeding present in milk; hyperexcitability and sedation reported; see also Breast-feeding, p. 218

Side-effects gastro-intestinal disturbances (including nausea, vomiting, diarrhoea, abdominal pain, and anorexia), weight loss; *less frequently* headache, fatigue, drowsiness, dizziness, hiccup, ataxia, euphoria, irritability, aggression, and impaired concentration; *rarely* tongue swelling, sleep disturbances, depression, psychosis, photophobia, dyskinesia, increased libido, vaginal bleeding, myopia, gingival hypertrophy, rash; *also reported* hyperactivity, increase in seizure frequency, blood disorders (including leucopenia, agranulocytosis, pancytopenia, and aplastic anaemia—blood counts required if features of infection), systemic lupus erythematosus, Stevens-Johnson syndrome; suicidal ideation

Indications and dose

Absence seizures, atypical absence, myoclonic seizures

• By mouth

Child 1 month–6 years initially 5 mg/kg (max. 125 mg) twice daily, increased every 5–7 days up to maintenance dose of 10–20 mg/kg (max. 500 mg) twice daily; total daily dose may rarely be given in 3 divided doses

Child 6–18 years initially 250 mg twice daily, increased by 250 mg at intervals of 5–7 days to usual dose of 500–750 mg twice daily; occasionally up to 1 g twice daily may be needed

Ethosuximide (Non-proprietary) (PoM)

Capsules, ethosuximide 250 mg, net price 56-cap pack = £48.20. Label: 8, counselling, blood disorders (see above), driving (see notes above)

Emeside® (Chemidex) (PoM)

Syrup, black currant, ethosuximide 250 mg/5 mL, net price 200-mL pack = £6.60. Label: 8, counselling, blood disorders (see above), driving (see notes above)

Zarontin® (Pfizer) (PoM)

Syrup, yellow, ethosuximide 250 mg/5 mL, net price 200-mL pack = £4.22. Label: 8, counselling, blood disorders (see above), driving (see notes above)

Gabapentin

Gabapentin is used as adjunctive therapy for the treatment of focal seizures with or without secondary generalisation; it is licensed as monotherapy in children over 12 years. It is not recommended if tonic, atonic, absence or myoclonic seizures are present.

GABAPENTIN

Cautions avoid abrupt withdrawal; diabetes mellitus; mixed seizures (including absences); false positive readings with some urinary protein tests; history of psychotic illness; high doses of oral solution in adolescents with low body-weight—see preparations below; **interactions**: Appendix 1 (gabapentin)

Renal impairment reduce dose if estimated glomerular filtration rate less than 80 mL/minute/1.73 m²; consult product literature

Pregnancy see Pregnancy, p. 218

Breast-feeding present in milk—manufacturer advises use only if potential benefit outweighs risk; see also Breast-feeding, p. 218

Side-effects nausea, vomiting, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence, weight gain, increased appetite, anorexia, hypertension, vasodilatation, oedema, dyspnoea, cough, hostility, confusion, emotional lability, depression, vertigo, anxiety, nervousness, abnormal thoughts, drowsiness, dizziness, malaise, ataxia, convulsions, movement disorders, speech disorder, amnesia, tremor, insomnia, headache, paraesthesia, nystagmus, abnormal reflexes, fever, flu syndrome, impotence, leucopenia, arthralgia, myalgia, twitching, visual disturbances, rhinitis, rash, pruritus, acne; *less commonly* palpitation; *also reported* pancreatitis, hepatitis, hallucinations, blood glucose fluctuations in children with diabetes, breast hypertrophy, gynaecomastia, acute renal failure, incontinence, thrombocytopenia, tinnitus, Stevens-Johnson syndrome, alopecia, hypersensitivity syndrome; suicidal ideation

Licensed use not licensed for use in children under 6 years; not licensed at doses over 50 mg/kg daily in children under 12 years

Indications and dose**Adjunctive treatment of focal seizures with or without secondary generalisation**• **By mouth**

Child 2–6 years 10 mg/kg once daily on day 1, then 10 mg/kg twice daily on day 2, then 10 mg/kg 3 times daily on day 3, increased according to response to usual dose of 30–70 mg/kg daily in 3 divided doses

Child 6–12 years 10 mg/kg (max. 300 mg) once daily on day 1, then 10 mg/kg (max. 300 mg) twice daily on day 2, then 10 mg/kg (max. 300 mg) 3 times daily on day 3; usual dose 25–35 mg/kg daily in 3 divided doses; max. 70 mg/kg daily in 3 divided doses

Child 12–18 years 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times daily on day 3 or initially 300 mg 3 times daily on day 1; then increased according to response in steps of 300 mg (in 3 divided doses) every 2–3 days; usual dose 0.9–3.6 g daily in 3 divided doses (max. 1.6 g 3 times daily)

Monotherapy for focal seizures with or without secondary generalisation• **By mouth**

Child 12–18 years 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times daily on day 3 or initially 300 mg 3 times daily on day 1; then increased according to response in steps of 300 mg (in 3 divided doses) every 2–3 days; usual dose 0.9–3.6 g daily in 3 divided doses (max. 1.6 g 3 times daily)

Note Some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate

Administration capsules can be opened but the bitter taste is difficult to mask

Gabapentin (Non-proprietary) (PoM)

Capsules, gabapentin 100 mg, net price 100-cap pack = £4.29; 300 mg, 100-cap pack = £6.64; 400 mg, 100-cap pack = £4.94. Label: 3, 5, 8, counselling, driving (see notes above)

Tablets, gabapentin 600 mg, net price 100-tab pack = £10.07; 800 mg, 100-tab pack = £34.04. Label: 3, 5, 8, counselling, driving (see notes above)

Oral solution, gabapentin 50 mg/mL, net price 150-mL pack = £57.50. Label: 3, 5, 8, counselling, driving (see notes above)

Excipients include propylene glycol (see Excipients, p. 2)

Important The levels of propylene glycol, acesulfame K and saccharin sodium may exceed the recommended WHO daily intake limits if high doses of gabapentin oral solution (Rosemont brand) are given to adolescents with low body-weight (39–50 kg)—consult product literature

Electrolytes Na^+ 0.031 mmol/mL, K^+ 0.097 mmol/mL

Neurontin® (Pfizer) (PoM)

Capsules, gabapentin 100 mg (white), net price 100-cap pack = £18.29; 300 mg (yellow), 100-cap pack = £42.40; 400 mg (orange), 100-cap pack = £49.06. Label: 3, 5, 8, counselling, driving (see notes above)

Tablets, f/c, gabapentin 600 mg, net price 100-tab pack = £84.80; 800 mg, 100-tab pack = £98.13. Label: 3, 5, 8, counselling, driving (see notes above)

Lacosamide

Lacosamide is licensed for adjunctive treatment of focal seizures with or without secondary generalisation.

The *Scottish Medicines Consortium* (p. 3) has advised (January 2009) that lacosamide (*Vimpat®*) is accepted for restricted use within NHS Scotland as adjunctive treatment for focal seizures with or without secondary generalisation in patients from 16 years. It is restricted for specialist use in refractory epilepsy.

LACOSAMIDE

Cautions risk of PR-interval prolongation (including conduction problems, severe cardiac disease, and concomitant use of drugs that prolong PR interval); interactions: Appendix 1 (lacosamide)

Contra-indications second- or third-degree AV block

Hepatic impairment titrate with caution in mild to moderate impairment if co-existing renal impairment; caution in severe impairment—no information available

Renal impairment loading dose regimen can be considered in mild to moderate impairment—titrate above 200 mg with caution; titrate with caution in severe impairment, max. 250 mg daily; consult product literature for loading dose if estimated glomerular filtration rate is less than 30 mL/minute/1.73 m²

Pregnancy see Pregnancy, p. 218

Breast-feeding manufacturer advises avoid—present in milk in animal studies; see also Breast-feeding, p. 218

Side-effects nausea, vomiting, constipation, flatulence, dizziness, headache, impaired coordination, cognitive disorder, drowsiness, tremor, depression, fatigue, abnormal gait, blurred vision, nystagmus, pruritus; rarely multi-organ hypersensitivity reaction (see Antiepileptic Hypersensitivity Syndrome, p. 217); also reported dyspepsia, dry mouth, AV block, bradycardia, PR-interval prolongation, atrial fibrillation, atrial flutter, aggression, agitation, psychosis, euphoria, confusion, hypoesthesia, dysarthria, irritability, agranulocytosis, muscle spasm, tinnitus, rash; suicidal ideation

Indications and dose**Adjunctive treatment of focal seizures with or without secondary generalisation**• **By mouth or by intravenous infusion over 15–60 minutes (for up to 5 days)**

Child 16–18 years initially 50 mg twice daily, increased weekly by 50 mg twice daily according to response and tolerability; initial maintenance dose 100 mg twice daily; max. 200 mg twice daily

Child 16–18 years alternative loading dose regimen (can be used under medical supervision when it is necessary to rapidly attain therapeutic plasma concentrations), initially 200 mg, followed 12 hours later by a maintenance dose of 100 mg twice daily; thereafter increased weekly by 50 mg twice daily according to response and tolerability; max. 200 mg twice daily

Administration for intravenous infusion, give undiluted or dilute with Glucose 5% or Sodium Chloride 0.9%

Vimpat® (UCB Pharma) (PoM)

Tablets, f/c, lacosamide 50 mg (pink), net price 14-tab pack = £10.81; 100 mg (yellow), 14-tab pack = £21.62, 56-tab pack = £86.50; 150 mg (salmon), 14-tab pack = £32.44, 56-tab pack £129.74; 200 mg (blue), 56-tab pack = £144.16. Label: 8, counselling, driving (see notes above)

Syrup, yellow-brown, sugar-free, strawberry flavoured, lacosamide 10 mg/mL, net price 200-mL pack = £25.74. Label: 8, counselling, driving (see notes above)

Excipients include aspartame (section 9.4.1), propylene glycol (see Excipients)

Electrolytes Na^+ 0.062 mmol/mL

Intravenous infusion, lacosamide 10 mg/mL net price 200-mg vial = £29.70

Electrolytes Na^+ 2.6 mmol/200-mg vial

Lamotrigine

Lamotrigine is an antiepileptic drug recommended as a first-line treatment for focal seizures and primary and secondary generalised tonic-clonic seizures. It is also licensed as monotherapy for typical absence seizures in children (but efficacy may not be maintained in all children). It may be tried as an adjunctive treatment for atonic and tonic seizures if first-line treatment has failed [unlicensed]. Myoclonic seizures may be exacerbated by lamotrigine and it can cause serious skin reactions; dose recommendations should be adhered to closely.

Lamotrigine is used either as sole treatment or as an adjunct to treatment with other antiepileptic drugs. Valproate increases plasma-lamotrigine concentration, whereas the enzyme-inducing antiepileptics reduce it; care is therefore required in choosing the appropriate initial dose and subsequent titration. When the potential for interaction is not known, treatment should be initiated with lower doses, such as those used with valproate.

LAMOTRIGINE

Cautions closely monitor and consider withdrawal if rash, fever, or signs of hypersensitivity syndrome develop; avoid abrupt withdrawal (taper off over 2 weeks or longer) unless serious skin reaction occurs; myoclonic seizures (may be exacerbated); **interactions**: see p. 217 and Appendix 1 (lamotrigine)

Blood disorders Children and their carers should be alert for symptoms and signs suggestive of bone-marrow failure, such as anaemia, bruising, or infection. Aplastic anaemia, bone-marrow depression, and pancytopenia have been associated rarely with lamotrigine

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history (see also MHRA/CHM advice, p. 216)

Hepatic impairment halve dose in moderate impairment; quarter dose in severe impairment

Renal impairment caution in renal failure; metabolite may accumulate; consider reducing maintenance dose in significant impairment

Pregnancy see Pregnancy, p. 218

Breast-feeding present in milk, but limited data suggest no harmful effect on infant; see also Breast-feeding, p. 218

Side-effects nausea, vomiting, diarrhoea, dry mouth, aggression, agitation, headache, drowsiness, dizzi-

ness, tremor, insomnia, ataxia, back pain, arthralgia, nystagmus, diplopia, blurred vision, rash (see Skin Reactions, below); *rarely* conjunctivitis; *very rarely* hepatic failure, movement disorders, unsteadiness, increase in seizure frequency, confusion, hallucination, blood disorders (including anaemia, leucopenia, thrombocytopenia, pancytopenia—see Blood Disorders, above), hypersensitivity syndrome (see Antiepileptic Hypersensitivity Syndrome, p. 217), lupus erythematosus-like reactions; *also reported* suicidal ideation, aseptic meningitis

Skin reactions Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have developed (especially in children); most rashes occur in the first 8 weeks. Rash is sometimes associated with hypersensitivity syndrome (see Side-effects, above) and is more common in patients with history of allergy or rash from other antiepileptic drugs. Consider withdrawal if rash or signs of hypersensitivity syndrome develop. Factors associated with increased risk of serious skin reactions include concomitant use of valproate, initial lamotrigine dosing higher than recommended, and more rapid dose escalation than recommended.

Counselling Warn children and their carers to see their doctor immediately if rash or signs or symptoms of hypersensitivity syndrome develop (see Antiepileptic Hypersensitivity Syndrome, p. 217)

Indications and dose

Monotherapy and adjunctive treatment of focal seizures and primary and secondary generalised tonic-clonic seizures; seizures associated with Lennox-Gastaut syndrome

• By mouth

Adjunctive therapy of seizures with valproate

Child 2–12 years initially 150 micrograms/kg once daily for 14 days (those weighing under 13 kg may receive 2 mg on alternate days for first 14 days) then 300 micrograms/kg once daily for further 14 days, thereafter increased by max. of 300 micrograms/kg every 7–14 days; usual maintenance 1–5 mg/kg daily in 1–2 divided doses; max. daily dose 200 mg

Child 12–18 years initially 25 mg on alternate days for 14 days then 25 mg daily for further 14 days, thereafter increased by max. 50 mg every 7–14 days; usual maintenance 100–200 mg daily in 1–2 divided doses

Adjunctive therapy of seizures (with enzyme inducing drugs) without valproate

Child 2–12 years initially 300 micrograms/kg twice daily for 14 days then 600 micrograms/kg twice daily for further 14 days, thereafter increased by max. 1.2 mg/kg every 7–14 days; usual maintenance 5–15 mg/kg daily in 1–2 divided doses; max. daily dose 400 mg

Child 12–18 years initially 50 mg daily for 14 days then 50 mg twice daily for further 14 days, thereafter increased by max. 100 mg every 7–14 days; usual maintenance 100–200 mg twice daily (up to 700 mg daily has been required)

Adjunctive therapy of seizures (without enzyme inducing drugs) without valproate

Child 2–12 years initially 300 micrograms/kg daily in 1–2 divided doses for 14 days then 600 micrograms/kg daily in 1–2 divided doses for further 14 days, thereafter increased by max. 600 micrograms/kg every 7–14 days; usual maintenance 1–10 mg/kg daily in 1–2 divided doses; max. 200 mg daily

Child 12–18 years initially 25 mg daily for 14 days, increased to 50 mg daily for further 14 days, then increased by max. 100 mg every 7–14 days; usual maintenance 100–200 mg daily in 1–2 divided doses

Monotherapy of seizures

Child 12–18 years initially 25 mg daily for 14 days, increased to 50 mg daily for further 14 days, then increased by max. 100 mg every 7–14 days; usual maintenance as monotherapy, 100–200 mg daily in 1–2 divided doses (up to 500 mg daily has been required)

Monotherapy of typical absence seizures

• By mouth

Child 2–12 years initially 300 micrograms/kg daily in 1–2 divided doses for 14 days, then 600 micrograms/kg daily in 1–2 divided doses for further 14 days, thereafter increased by max. 600 micrograms/kg every 7–14 days; usual maintenance 1–10 mg/kg daily in 1–2 divided doses (up to 15 mg/kg daily has been required)

Note Dose titration should be repeated if restarting after interval of more than 5 days

Safe Practice

Do not confuse the different combinations; see also notes above

Lamotrigine (Non-proprietary) (PoM)

Tablets, lamotrigine 25 mg, net price 56-tab pack = £1.38; 50 mg, 56-tab pack = £1.66; 100 mg, 56-tab pack = £2.17; 200 mg, 30-tab pack = £27.53, 56-tab pack = £3.39. Label: 8, counselling, driving (see notes above), skin reactions (see above)

Dispersible tablets, lamotrigine 5 mg, net price 28-tab pack = £1.64; 25 mg, 56-tab pack = £2.58; 100 mg, 56-tab pack = £4.32. Label: 8, 13, counselling, driving (see notes above), skin reactions (see above)

Note Patients may need to be maintained on a specific manufacturer's branded or generic lamotrigine product, see MHRA/CHM advice, p. 216

Lamictal® (GSK) (PoM)

Tablets, yellow, lamotrigine 25 mg, net price 56-tab pack = £19.61; 50 mg, 56-tab pack = £33.35; 100 mg, 56-tab pack = £57.53; 200 mg, 56-tab pack = £97.79. Label: 8, counselling, driving (see notes above), skin reactions (see above)

Dispersible tablets, chewable, lamotrigine 2 mg, net price 30-tab pack = £10.45; 5 mg, 28-tab pack = £7.82; 25 mg, 56-tab pack = £19.61; 100 mg, 56-tab pack = £57.53. Label: 8, 13, counselling, driving (see notes above), skin reactions (see above)

Note Patients may need to be maintained on a specific manufacturer's branded or generic lamotrigine product, see MHRA/CHM advice, p. 216

Levetiracetam

Levetiracetam is used for monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation, and for adjunctive treatment of myoclonic seizures in children with juvenile myoclonic epilepsy and primary generalised tonic-clonic seizures. Levetiracetam may also be prescribed alone and in combination for the treatment of myoclonic seizures, and under specialist supervision for absence seizures [both unlicensed].

LEVETIRACETAM

Cautions avoid abrupt withdrawal; **interactions:** Appendix 1 (levetiracetam)

Hepatic impairment halve dose in severe hepatic impairment if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²

Renal impairment reduce dose if estimated glomerular filtration rate less than 80 mL/minute/1.73 m² (consult product literature)

Pregnancy see Pregnancy, p. 218

Breast-feeding present in milk—manufacturer advises avoid; see also Breast-feeding, p. 218

Side-effects anorexia, weight changes, abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, cough, drowsiness, amnesia, ataxia, convulsion, dizziness, headache, tremor, hyperkinesia, malaise, impaired attention, aggression, agitation, depression, insomnia, anxiety, irritability, personality disorder, thrombocytopenia, myalgia, diplopia, blurred vision, rash; *also reported* pancreatitis, hepatic failure, paraesthesia, confusion, hallucinations, psychosis, suicidal ideation, leucopenia, neutropenia, pancytopenia, alopecia, toxic epidermal necrolysis, Stevens-Johnson syndrome

Licensed use *granules* not licensed for use in children under 6 years, for initial treatment in children with body-weight less than 25 kg, or for the administration of doses below 250 mg

Indications and dose

Monotherapy of focal seizures

• By mouth or by intravenous infusion

Note If switching between oral therapy and intravenous therapy (for those temporarily unable to take oral medication), the intravenous dose should be the same as the established oral dose

Child 16–18 years initially 250 mg once daily increased after 1 week to 250 mg twice daily; thereafter, increased according to response in steps of 250 mg twice daily every 2 weeks; max. 1.5 g twice daily

Adjunctive therapy of focal seizures

• By mouth

Child 1–6 months initially 7 mg/kg once daily, increased by max. 7 mg/kg twice daily every 2 weeks; max. 21 mg/kg twice daily

Child 6 months–18 years, body-weight under 50 kg initially 10 mg/kg once daily, increased by max. 10 mg/kg twice daily every 2 weeks; max. 30 mg/kg twice daily

Child 12–18 years, body-weight over 50 kg initially 250 mg twice daily, increased by 500 mg twice daily every 2 weeks; max. 1.5 g twice daily

• By intravenous infusion

Note If switching between oral therapy and intravenous therapy (for those temporarily unable to take oral medication), the intravenous dose should be the same as the established oral dose

Child 4–18 years, body-weight under 50 kg initially 10 mg/kg once daily, increased by max. 10 mg/kg twice daily every 2 weeks; max. 30 mg/kg twice daily

Child 12–18 years, body-weight over 50 kg initially 250 mg twice daily, increased by 500 mg twice daily every 2 weeks; max. 1.5 g twice daily

Adjunctive therapy of myoclonic seizures and tonic-clonic seizures

• By mouth or by intravenous infusion

Note If switching between oral therapy and intravenous therapy (for those temporarily unable to take oral medication), the intravenous dose should be the same as the established oral dose

Child 12–18 years, body-weight under 50 kg initially 10 mg/kg once daily, increased by max. 10 mg/kg twice daily every 2 weeks; max. 30 mg/kg twice daily

Child 12–18 years, body-weight over 50 kg initially 250 mg twice daily, increased by 500 mg twice daily every 2 weeks; max. 1.5 g twice daily

Administration for *intravenous infusion*, dilute requisite dose with at least 100 mL Glucose 5% or Sodium Chloride 0.9%; give over 15 minutes

For administration of *oral solution*, requisite dose may be diluted in a glass of water

Levetiracetam (Non-proprietary) (PoM)

Tablets, levetiracetam 250 mg, net price 60-tab pack = £1.79; 500 mg, 60-tab pack = £3.23; 750 mg, 60-tab pack = £4.24; 1 g, 60-tab pack = £4.89. Label: 8

Oral Solution, levetiracetam 100 mg/mL, net price 300 mL = £27.64. Label: 8

Brands include Desitrend®

Granules, levetiracetam 250 mg/sachet, net price 60-sachet pack = £22.41; 500 mg/sachet, net price 60-sachet pack = £39.46; 1 g/sachet, net price 60-sachet pack = £76.27. Label: 8

Brands include Desitrend®

Keppra® (UCB Pharma) (PoM)

Tablets, f/c, levetiracetam 250 mg (blue), net price 60-tab pack = £28.01; 500 mg (yellow), 60-tab pack = £49.32; 750 mg (orange), 60-tab pack = £84.02; 1 g (white), 60-tab pack = £95.34. Label: 8

Oral solution, sugar-free, levetiracetam 100 mg/mL, net price 150 mL (with 1-mL or 3-mL syringe) = £33.48, 300 mL (with 10-mL syringe) = £66.95. Label: 8

Concentrate for intravenous infusion, levetiracetam 100 mg/mL, net price 5-mL vial = £12.73

Electrolytes Na⁺ 0.83 mmol/vial

Note For dilution before use

Perampanel

Perampanel is licensed for adjunctive treatment of focal seizures with or without secondary generalised seizures.

PERAMPANEL

Cautions interactions: Appendix 1 (perampanel)

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history (see also MHRA/CHM advice, p. 216)

Hepatic impairment increase at intervals of at least 2 weeks, up to max. 8 mg daily in mild or moderate impairment; avoid in severe impairment

Renal impairment avoid in moderate or severe impairment

Pregnancy see Pregnancy, p. 218; manufacturer advises avoid

Breast-feeding avoid—present in milk in *animal studies*

Side-effects nausea, changes in appetite, weight increase, aggression, dizziness, drowsiness, dysarthria, gait disturbance, irritability, anxiety, confusion, suicidal ideation and behaviour, malaise, ataxia, back pain, vertigo, blurred vision, diplopia

Indications and dose**Adjunctive treatment of partial onset seizures with or without secondary generalised seizures**

• By mouth

Child 12–18 years initially 2 mg once daily before bedtime, increased according to response and tolerability in 2-mg steps at intervals of at least 2 weeks; usual maintenance 4–8 mg once daily; max. 12 mg once daily

Note Titrate at intervals of at least 1 week with concomitant carbamazepine, oxcarbazepine, or phenytoin (see also Appendix 1).

Fycompa® (Eisai) ▼ (PoM)

Tablets, all f/c, perampanel 2 mg (orange), net price 7-tab pack = £35.00; 4 mg (red) 28-tab pack = £140.00; 6 mg (pink) 28-tab pack = £140.00; 8 mg (purple) 28-tab pack = £140.00; 10 mg (green) 28-tab pack = £140.00; 12 mg (blue) 28-tab pack = £140.00. Label: 3, 8, 25, counselling, anxiety (see notes above)

Note Patients may need to be maintained on a specific manufacturer's branded or generic perampanel product, see MHRA/CHM advice, p. 216

Phenobarbital and primidone

Phenobarbital is effective for tonic-clonic, focal seizures and neonatal seizures but may cause behavioural disturbances and hyperkinesia. It may be tried for atypical absence, atonic, and tonic seizures. For therapeutic purposes phenobarbital and phenobarbital sodium should be considered equivalent in effect. Rebound seizures may be a problem on withdrawal. Monitoring the plasma-drug concentration is less useful than with other drugs because tolerance occurs.

Primidone is largely converted to phenobarbital and this is probably responsible for its antiepileptic action. It is used rarely in children. A low initial dose of primidone is essential.

PHENOBARBITAL
(Phenobarbitone)

Cautions see also notes above; debilitated; respiratory depression (avoid if severe); avoid abrupt withdrawal (dependence with prolonged use); history of drug and alcohol abuse; consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium; avoid in acute porphyria (see section 9.8.2); interactions: see p. 217 and Appendix 1 (phenobarbital)

Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients should be maintained on a specific manufacturer's product (see also MHRA/CHM advice, p. 216)

Hepatic impairment may precipitate coma; avoid in severe impairment

Renal impairment use with caution

Pregnancy see Pregnancy, p. 218

Breast-feeding avoid if possible; drowsiness may occur; see also Breast-feeding, p. 218

Side-effects hepatitis, cholestasis; hypotension; respiratory depression; drowsiness, lethargy, depression, ataxia, behavioural disturbances, nystagmus, irritability, hallucinations, impaired memory and cognition, hyperactivity; osteomalacia (see Cautions); megaloblastic anaemia (may be treated with folic acid), agranulocytosis, thrombocytopenia; allergic skin reactions; *very rarely* Stevens-Johnson syndrome and toxic epidermal necrolysis; suicidal ideation; Antiepileptic Hypersensitivity Syndrome (see p. 217); **overdose**: see Emergency Treatment of Poisoning, p. 24

Pharmacokinetics trough plasma concentration for optimum response 15–40 mg/litre (60–180 micromol/litre)

Indications and dose

All forms of epilepsy except typical absence seizures

• By mouth or by intravenous injection

Neonate initially 20 mg/kg by slow intravenous injection then 2.5–5 mg/kg once daily either by slow intravenous injection or by mouth; dose and frequency adjusted according to response

• By mouth

Child 1 month–12 years initially 1–1.5 mg/kg twice daily, increased by 2 mg/kg daily as required; usual maintenance dose 2.5–4 mg/kg once or twice daily

Child 12–18 years 60–180 mg once daily

Status epilepticus section 4.8.2

Note For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect.

Administration for administration by mouth, tablets may be crushed

For intravenous injection, dilute to a concentration of 20 mg/mL with Water for Injections; give over 20 minutes (no faster than 1 mg/kg/minute)

Phenobarbital (Non-proprietary) CB3

Tablets, phenobarbital 15 mg, net price 28-tab pack = £22.29; 30 mg, 28-tab pack = 84p; 60 mg, 28-tab pack = £6.90. Label: 2, 8, counselling, driving (see notes above)

Elixir, phenobarbital 15 mg/5 mL in a suitable flavoured vehicle, containing alcohol 38%, net price 100 mL = £4.67. Label: 2, 8, counselling, driving (see notes above)

Note Some hospitals supply alcohol-free formulations of varying phenobarbital strengths

Note Patients should be maintained on a specific manufacturer's branded or generic oral phenobarbital product. See also MHRA/CHM advice, p. 216

Injection, phenobarbital sodium 15 mg/mL, net price 1-mL amp = £1.97; 30 mg/mL, 1-mL amp = £3.50; 60 mg/mL, 1-mL amp = £3.73; 200 mg/mL, 1-mL amp = £4.36

Excipients include propylene glycol (see Excipients, p. 2)

Note Must be diluted before intravenous administration (see Administration)

PRIMIDONE

Cautions see Phenobarbital; **interactions**: see p. 217 and Appendix 1 (phenobarbital)

Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients should be maintained on a specific manufacturer's product (see also MHRA/CHM advice, p. 216)

Hepatic impairment reduce dose, may precipitate coma

Renal impairment see Phenobarbital

Pregnancy see Pregnancy, p. 218

Breast-feeding see Breast-feeding, p. 218

Side-effects see Phenobarbital; also nausea, visual disturbances; *less commonly* vomiting, headache, dizziness; *rarely* psychosis, lupus erythematosus, arthralgia; *also reported* Dupuytren's contracture

Pharmacokinetics monitor plasma concentrations of derived phenobarbital. Optimum range as for phenobarbital

Indications and dose

All forms of epilepsy except typical absence seizures (but see notes above)

• By mouth

Child under 2 years initially 125 mg daily at bedtime, increased by 125 mg every 3 days according to response; usual maintenance, 125–250 mg twice daily

Child 2–5 years initially 125 mg daily at bedtime, increased by 125 mg every 3 days according to response; usual maintenance, 250–375 mg twice daily

Child 5–9 years initially 125 mg daily at bedtime, increased by 125 mg every 3 days according to response; usual maintenance, 375–500 mg twice a day

Child 9–18 years initially 125 mg daily at bedtime, increased by 125 mg every 3 days to 250 mg twice daily, then increased according to response by 250 mg every 3 days to max. 750 mg twice daily

Primidone (Non-proprietary) P0M

Tablets, primidone 50 mg, net price 100-tab pack = £41.96; 250 mg, 100-tab pack = £48.46. Label: 2, 8, counselling, driving (see notes above)

Note Patients being treated for epilepsy should be maintained on a specific manufacturer's branded or generic primidone product. See also MHRA/CHM advice, p. 216

Phenytoin

Phenytoin is licensed for tonic-clonic and focal seizures but may exacerbate absence or myoclonic seizures and should be avoided if these seizures are present. It has a narrow therapeutic index and the relationship between dose and plasma-drug concentration is non-linear; small dosage increases in some children may produce large increases in plasma-drug concentration with acute toxic side-effects. Similarly, a few missed doses or a small change in drug absorption may result in a marked change in plasma-drug concentration. Monitoring of plasma-drug concentration improves dosage adjustment.

Preparations containing phenytoin sodium are **not** bioequivalent to those containing phenytoin base (such as *Epanutin Infatabs*® and *Epanutin*® suspension); 100 mg of phenytoin sodium is approximately equivalent in therapeutic effect to 92 mg phenytoin base. The dose is the same for all phenytoin products when initiating therapy, however if switching between these products the difference in phenytoin content may be clinically significant. Care is needed when making changes between formulations and plasma-phenytoin concentration monitoring is recommended (see also MHRA/CHM advice, p. 216).

Symptoms of phenytoin toxicity include nystagmus, diplopia, slurred speech, ataxia, confusion, and hyperglycaemia.

Phenytoin may cause coarsening of the facial appearance, acne, hirsutism, and gingival hyperplasia and so may be particularly undesirable in adolescent patients.

When only parenteral administration is possible, **fosphenytoin** (section 4.8.2), a pro-drug of phenytoin, may be convenient to give. Whereas phenytoin should be given intravenously only, fosphenytoin may also be given by intramuscular injection.

PHENYTOIN

Cautions see notes above; cross-sensitivity reported with carbamazepine (see also Antiepileptic Hypersensitivity Syndrome, p. 217); avoid abrupt withdrawal; HLA-B* 1502 allele in individuals of Han Chinese or Thai origin—avoid unless essential (increased risk of Stevens–Johnson syndrome); manufacturer recommends blood counts (but evidence of practical value uncertain); consider vitamin D supplementation in patients that are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium; enteral feeding (interrupt feeding for 2 hours before and after dose; more frequent monitoring may be necessary); avoid in acute porphyria (section 9.8.2); **interactions:** see p. 217 and Appendix 1 (phenytoin)

Blood or skin disorders Children and their carers should be told how to recognise signs of blood or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. Leucopenia which is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative)

Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients should be maintained on a specific manufacturer's product (see also MHRA/CHM advice, p. 216)

Hepatic impairment reduce dose

Pregnancy changes in plasma-protein binding make interpretation of plasma-phenytoin concentrations difficult—monitor unbound fraction; see also Pregnancy, p. 218

Breast-feeding small amounts present in milk, but not known to be harmful; see also Breast-feeding, p. 218

Side-effects nausea, vomiting, constipation; drowsiness, insomnia, transient nervousness, tremor, paraesthesia, dizziness, headache, anorexia; gingival hypertrophy and tenderness (maintain good oral hygiene); rash (discontinue; if mild reintroduce cautiously but discontinue immediately if recurrence), acne, hirsutism, coarsening of facial appearance; rarely hepatotoxicity (discontinue immediately and do not readminister), peripheral neuropathy, dyskinesia, lymphadenopathy, osteomalacia (see Cautions), blood disorders (including megaloblastic anaemia, leucopenia, thrombocytopenia, and aplastic anaemia), polyarteritis nodosa, lupus erythematosus, Stevens–Johnson syndrome, and toxic epidermal necrolysis; also reported polyarthropathy, pneumonitis, interstitial nephritis, hypersensitivity syndrome (see Antiepileptic Hypersensitivity Syndrome, p. 217), suicidal ideation

Pharmacokinetics therapeutic plasma-phenytoin concentrations reduced in first 3 months of life because of reduced protein binding.
Trough plasma concentration for optimum response:

Neonate–3 months, 6–15 mg/litre (25–60 micromol/litre)

Child 3 months–18 years, 10–20 mg/litre (40–80 micromol/litre)

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Tonic-clonic seizures, focal seizures

- By intravenous injection (over 20–30 minutes) and by mouth

Neonate initial loading dose by slow intravenous injection (section 4.8.2) 18 mg/kg then by mouth 2.5–5 mg/kg twice daily adjusted according to response and plasma-phenytoin concentration (usual max. 7.5 mg/kg twice daily)

- By mouth

Child 1 month–12 years initially 1.5–2.5 mg/kg twice daily, then adjusted according to response and plasma-phenytoin concentration to 2.5–5 mg/kg twice daily (usual max. 7.5 mg/kg twice daily or 300 mg daily)

Child 12–18 years initially 75–150 mg twice daily then adjusted according to response and plasma-phenytoin concentration to 150–200 mg twice daily (usual max. 300 mg twice daily)

Status epilepticus, acute symptomatic seizures associated with head trauma or neurosurgery section 4.8.2

Administration for administration by mouth, interrupt enteral feeds for at least 1–2 hours before and after giving phenytoin; give with water to enhance absorption

For administration by intravenous injection and intravenous infusion, see p. 239

Phenytoin (Non-proprietary) (PoM)

Tablets, coated, phenytoin sodium 100 mg, net price 28-tab pack = £30.00. Label: 8, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Capsules, phenytoin sodium 25 mg, net price 28-cap pack = £15.74; 50 mg, 28-cap pack = £15.98; 100 mg, 84-cap pack = £67.50; 300 mg, 28-cap pack = £67.50. Label: 8, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Note Patients should be maintained on a specific manufacturer's branded or generic phenytoin product. See also MHRA/CHM advice, p. 216

Epanutin® (Pfizer) (PoM)

Chewable tablets (*Infatabs*®), yellow, scored, phenytoin 50 mg, net price 200-tab pack = £13.18. Label: 8, 24, counselling, blood or skin disorder symptoms (see above), driving (see notes above)

Suspension, red, phenytoin 30 mg/5 mL, net price 500 mL = £4.27. Label: 8, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Note Patients should be maintained on a specific manufacturer's branded or generic phenytoin product, see MHRA/CHM advice, p. 216 For additional information regarding differences in bioavailability of preparations containing phenytoin base and phenytoin sodium see notes above, p. 227

Parenteral preparations

Section 4.8.2

Rufinamide

Rufinamide is licensed for the adjunctive treatment of seizures in Lennox-Gastaut syndrome. It may be considered by a tertiary specialist for the treatment of refractory tonic or atonic seizures [unlicensed].

The *Scottish Medicines Consortium* (p. 3) has advised (October 2008) that rufinamide (*Inovelon*[®]) is accepted for restricted use within NHS Scotland as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years and above. It is restricted for use when alternative traditional antiepileptic drugs are unsatisfactory.

RUFINAMIDE

Cautions closely monitor and consider withdrawal if rash, fever, or other signs of hypersensitivity syndrome develop (see also Antiepileptic Hypersensitivity Syndrome, p. 217); avoid abrupt withdrawal; **interactions:** see p. 217 and Appendix 1 (rufinamide)

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history (see also MHRA/CHM advice, p. 216)

Hepatic impairment caution and careful dose titration in mild to moderate impairment; avoid in severe impairment

Pregnancy see Pregnancy, p. 218

Breast-feeding manufacturer advises avoid—no information available; see also Breast-feeding, p. 218

Side-effects nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain; rhinitis, epistaxis; weight loss, anorexia, dizziness, headache, drowsiness, insomnia, anxiety, fatigue, increase in seizure frequency, impaired coordination, hyperactivity, tremor, gait disturbances; influenza-like symptoms; oligomenorrhoea; back pain; nystagmus, diplopia, blurred vision; rash, and acne; hypersensitivity syndrome (see Antiepileptic Hypersensitivity Syndrome, p. 217) also reported

Indications and dose

Adjunctive treatment of seizures in Lennox-Gastaut syndrome

• By mouth

Child 4–18 years body-weight less than 30 kg, initially 100 mg twice daily increased according to response in steps of 100 mg twice daily up to every 2 days; max. 500 mg twice daily (max. 300 mg twice daily if adjunctive therapy with valproate)

Child 4–18 years body-weight over 30 kg, initially 200 mg twice daily increased according to response in steps of 200 mg twice daily up to every 2 days; body-weight 30–50 kg max. 900 mg twice daily; body-weight 50–70 kg max. 1.2 g twice daily; body-weight over 70 kg max. 1.6 g twice daily

Administration Tablets may be crushed and given in half a glass of water

Inovelon[®] (Eisai) (PoM)

Tablets, pink, f/c, scored, rufinamide 100 mg, net price 10-tab pack = £5.15; 200 mg, 60-tab pack = £61.77; 400 mg, 60-tab pack = £102.96. Label: 8, 21, counselling, driving (see notes above), hypersensitivity syndrome (see notes above)

Oral suspension, white, sugar-free, rufinamide 40 mg/mL, net price 460-mL pack = £94.71. Label: 8, 21, counselling, driving (see notes above), hypersensitivity syndrome (see notes above)

Excipients include propylene glycol

Note Patients may need to be maintained on a specific manufacturer's branded or generic rufinamide product, see MHRA/CHM advice, p. 216

Stiripentol

Stiripentol is licensed for use in combination with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in children with severe myoclonic epilepsy in infancy (Dravet Syndrome). It should be used under specialist supervision.

STIRIPENTOL

Cautions perform full blood count and liver function tests prior to initiating treatment and every 6 months thereafter; monitor growth; **interactions:** Appendix 1 (stiripentol)

Contra-indications history of psychosis

Hepatic impairment avoid—no information available

Renal impairment avoid—no information available

Pregnancy see Pregnancy, p. 218

Breast-feeding present in milk in *animal* studies; see also Breast-feeding, p. 218

Side-effects nausea, vomiting; aggression, anorexia, ataxia, drowsiness, dystonia, hyperexcitability, hyperkinesia, hypotonia, irritability, sleep disorders, weight loss; neutropenia; *less commonly* fatigue, photosensitivity, rash, and urticaria

Indications and dose

Severe myoclonic epilepsy in infancy

• By mouth

Child 3–18 years initially 10 mg/kg in 2–3 divided doses; titrate dose over minimum of 3 days to max. 50 mg/kg/day in 2–3 divided doses

Diacomit[®] (Alan Pharmaceuticals) ▼ (PoM)

Capsules, stiripentol 250 mg (pink), net price 60-cap pack = £284.00; 500 mg (white), 60-cap pack = £493.00. Label: 1, 8, 21, counselling, administration

Powder, stiripentol 250 mg, net price 60-sachet pack = £284.00; 500 mg, 60-sachet pack = £493.00.

Label: 1, 8, 13, 21, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling Do not take with milk, dairy products, carbonated drinks, fruit juice, or with food or drink that contains caffeine

Tiagabine

Tiagabine is used as adjunctive treatment for focal seizures with or without secondary generalisation that are not satisfactorily controlled by other antiepileptics. It should be avoided in absence, myoclonic, tonic and atonic seizures due to risk of seizure exacerbation.

TIAGABINE

Cautions avoid in acute porphyria (section 9.8.2); avoid abrupt withdrawal; **interactions:** Appendix 1 (tiagabine)

Driving May impair performance of skilled tasks (e.g. driving)

Hepatic impairment in mild to moderate impairment reduce dose, prolong the dose interval, or both; avoid in severe impairment

Pregnancy see Pregnancy, p. 218

Breast-feeding see Breast-feeding, p. 218

Side-effects diarrhoea; dizziness, tiredness, nervousness, tremor, impaired concentration, emotional lability, speech impairment; *rarely* confusion, depression, drowsiness, psychosis, non-convulsive status epilepticus, bruising, and visual disturbances; suicidal ideation; leucopenia also reported

Indications and dose

Adjunctive treatment for focal seizures with or without secondary generalisation not satisfactorily controlled by other antiepileptics

• By mouth

With enzyme-inducing drugs

Child 12–18 years initially 5–10 mg daily in 1–2 divided doses, increased in steps of 5–10 mg daily at weekly intervals; usual maintenance dose 30–45 mg daily in 2–3 divided doses

Without enzyme-inducing drugs

Child 12–18 years initially 5–10 mg daily in 1–2 divided doses, increased in steps of 5–10 mg daily at weekly intervals; initial maintenance dose 15–30 mg daily in 2–3 divided doses

Gabitril® (TEVA UK) (POM)

Tablets, f/c, tiagabine (as hydrochloride) 5 mg, net price 100-tab pack = £52.04; 10 mg, 100-tab pack = £104.09; 15 mg, 100-tab pack = £156.13. Label: 21

Topiramate

Topiramate can be given alone or as adjunctive treatment in generalised tonic-clonic seizures or focal seizures. It can also be used for absence, tonic and atonic seizures under specialist supervision and as an option in myoclonic seizures [all unlicensed]. Topiramate is also licensed for prophylaxis of migraine (section 4.7.4.2).

TOPIRAMATE

Cautions avoid abrupt withdrawal; risk of metabolic acidosis; risk of nephrolithiasis—ensure adequate hydration (especially in strenuous activity or warm environment); avoid in acute porphyria (section 9.8.2); **interactions:** see p. 217 and Appendix 1 (topiramate)

Important Topiramate has been associated with acute myopia with secondary angle-closure glaucoma, typically occurring within 1 month of starting treatment. Choroidal effusions resulting in anterior displacement of the lens and iris have also been reported. If raised intra-ocular pressure occurs:

- seek specialist ophthalmological advice;
- use appropriate measures to reduce intra-ocular pressure;
- stop topiramate as rapidly as feasible

Switching between formulations Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history (see also MHRA/CHM advice, p. 216)

Hepatic impairment use with caution in moderate to severe impairment—clearance may be reduced

Renal impairment use with caution; half usual starting and maintenance dose if estimated glomerular filtration rate less than 70 mL/minute/1.73m²—reduced clearance and longer time to steady-state plasma concentration

Pregnancy see Pregnancy, p. 218

Breast-feeding manufacturer advises avoid—present in milk; see also Breast-feeding, p. 218

Side-effects nausea, diarrhoea, vomiting, constipation, dyspepsia, abdominal pain, dry mouth, taste disturbance, gastritis, appetite changes, dyspnoea, impaired attention, cognitive impairment, movement disorders, seizures, tremor, malaise, impaired coordination, speech disorder, drowsiness, dizziness, sleep disturbance, anxiety, confusion, paraesthesia, aggression, mood changes, depression, agitation, irritability, nephrolithiasis, urinary disorders, anaemia, arthralgia, muscle spasm, myalgia, muscular weakness, visual disturbances, nystagmus, tinnitus, epis-taxis, alopecia, rash, pruritus; *less commonly* pancreatitis, flatulence, abdominal distension, gingival bleeding, salivation, halitosis, thirst, glossodynia, bradycardia, palpitation, hypotension, postural hypotension, flushing, altered sense of smell, peripheral neuropathy, suicidal ideation, psychosis, panic attack, influenza-like symptoms, sexual dysfunction, urinary calculus, haematuria, blood disorders (including leucopenia, neutropenia, and thrombocytopenia), hypokalaemia, metabolic acidosis, dry eye, photophobia, blepharospasm, increased lacrimation, mydriasis, hearing loss, reduced sweating, skin discoloration; *rarely* hepatitis, hepatic failure, Raynaud's syndrome, periorbital oedema, unilateral blindness, Stevens-Johnson syndrome, abnormal skin odour, calcinosis; *very rarely* angle-closure glaucoma; *also reported* encephalopathy, hyperammonaemia, maculopathy, toxic epidermal necrolysis

Licensed use not licensed for use in children for migraine prophylaxis

Indications and dose

Monotherapy of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation

• By mouth

Child 6–18 years initially 0.5–1 mg/kg (max. 25 mg) at night for 1 week then increased in steps of 250–500 micrograms/kg (max. 25 mg) twice daily at intervals of 1–2 weeks; initial target dose 50 mg twice daily; max. 7.5 mg/kg (max. 250 mg) twice daily

Adjunctive treatment of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation, adjunctive treatment of seizures in Lennox-Gastaut syndrome

• By mouth

Child 2–18 years initially 1–3 mg/kg (max. 25 mg) at night for 1 week then increased in steps of 0.5–1.5 mg/kg (max. 25 mg) twice daily at intervals of 1–2 weeks; usual dose 2.5–4.5 mg/kg twice daily; max. 7.5 mg/kg (max. 200 mg) twice daily

Migraine prophylaxis• **By mouth**

Child 16–18 years initially 25 mg at night for 1 week then increased in steps of 25 mg daily at weekly intervals; usual dose 50–100 mg daily in 2 divided doses; max. 200 mg daily

Note If child cannot tolerate titration regimens recommended above then smaller steps or longer interval between steps may be used

Topiramate (Non-proprietary) (PoM)

Tablets, topiramate 25 mg, net price 60-tab pack = £3.24; 50 mg, 60-tab pack = £2.94; 100 mg, 60-tab pack = £2.95; 200 mg, 60-tab pack = £16.25. Label: 3, 8, counselling, driving (see notes above)

Capsules, topiramate 15 mg, net price 60-cap pack = £19.63; 25 mg, 60-cap pack = £13.26; 50 mg, 60-cap pack = £44.56. Label: 3, 8, counselling, driving (see notes above)

Note Patients being treated for epilepsy may need to be maintained on a specific manufacturer's branded or generic topiramate product, see MHRA/CHM advice, p. 216

Topamax® (Janssen) (PoM)

Tablets, f/c, topiramate 25 mg, net price 60-tab pack = £19.29; 50 mg (light yellow), 60-tab pack = £31.69; 100 mg (yellow), 60-tab pack = £56.76; 200 mg (salmon), 60-tab pack = £110.23. Label: 3, 8, counselling, driving (see notes above)

Sprinkle capsules, topiramate 15 mg, net price 60-cap pack = £14.79; 25 mg, 60-cap pack = £22.18; 50 mg, 60-cap pack = £36.45. Label: 3, 8, counselling, administration, driving (see notes above)

Counselling Swallow whole or sprinkle contents of capsule on soft food and swallow immediately without chewing

Note Patients being treated for epilepsy may need to be maintained on a specific manufacturer's branded or generic topiramate product, see MHRA/CHM advice, p. 216

Valproate

Valproate (as either sodium valproate or valproic acid) is effective in controlling tonic-clonic seizures, particularly in primary generalised epilepsy. It is a drug of choice in primary generalised tonic-clonic seizures, focal seizures, generalised absences and myoclonic seizures, and can be tried in atypical absence seizures. It is recommended as a first-line option in atonic and tonic seizures. Valproate should generally be avoided in children under 2 years especially with other antiepileptics, but it may be required in infants with continuing epileptic tendency. Sodium valproate has widespread metabolic effects, and monitoring of liver function tests and full blood count is essential (see Cautions below). Plasma-valproate concentrations are not a useful index of efficacy, therefore routine monitoring is unhelpful. Valproate is associated with teratogenic risks—these should be fully discussed before prescribing for young women of child-bearing age (see Pregnancy, p. 218).

SODIUM VALPROATE

Cautions see notes above; monitor liver function before therapy and during first 6 months especially in children most at risk (see also below); measure full blood count and ensure no undue potential for bleeding before starting and before surgery; systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal; consider vitamin D supplementation in patients that are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium; **interactions:** see p. 217 and Appendix 1 (valproate)

Liver toxicity Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in first 6 months and usually involving multiple antiepileptic therapy. Raised liver enzymes during valproate treatment are usually transient but children should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—discontinue if abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities)

Blood or hepatic disorders Children and their carers should be told how to recognise signs of blood or liver disorders and advised to seek immediate medical attention if symptoms develop

Pancreatitis Children and their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea, or vomiting develop; discontinue if pancreatitis is diagnosed

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history (see also MHRA/CHM advice, p. 216)

Contra-indications family history of severe hepatic dysfunction; acute porphyria (section 9.8.2)

Hepatic impairment avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months); avoid in active liver disease; see also under Cautions

Renal impairment reduce dose

Pregnancy see Pregnancy, p. 218; neonatal bleeding (related to hypofibrinaemia) and neonatal hepatotoxicity also reported

Breast-feeding amount too small to be harmful; see also Breast-feeding, p. 218

Side-effects nausea, gastric irritation, diarrhoea; weight gain; hyperammonaemia, thrombocytopenia; transient hair loss (regrowth may be curly); *less frequently* increased alertness, aggression, hyperactivity, behavioural disturbances, ataxia, tremor, and vasculitis; *rarely* hepatic dysfunction (see under Cautions); withdraw treatment immediately if persistent vomiting and abdominal pain, anorexia, jaundice, oedema, malaise, drowsiness, or loss of seizure control; lethargy, drowsiness, confusion, stupor, hallucinations, blood disorders (including anaemia, leucopenia, and pancytopenia), hearing loss, and rash; *very rarely* pancreatitis (see under Cautions), peripheral oedema, increase in bleeding time, extrapyramidal symptoms, encephalopathy, coma, gynaecomastia, Fanconi's syndrome, hirsutism, enuresis, hyponatraemia, acne, toxic epidermal necrolysis, and Stevens-Johnson syndrome; suicidal ideation; reduced bone mineral density (see Cautions); *also reported* menstrual disturbances, male infertility, syndrome of inappropriate secretion of antidiuretic hormone, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, hypersensitivity reactions

Indications and dose**All forms of epilepsy**• **By mouth or by rectum**

Neonate initially 20 mg/kg once daily; usual maintenance dose 10 mg/kg twice daily

Child 1 month–12 years initially 10–15 mg/kg (max. 600 mg) daily in 1–2 divided doses; usual maintenance dose 25–30 mg/kg daily in 2 divided doses (up to 60 mg/kg daily in 2 divided doses in

infantile spasms; monitor clinical chemistry and haematological parameters if dose exceeds 40 mg/kg daily)

Child 12–18 years initially 600 mg daily in 1–2 divided doses increased gradually (in steps of 150–300 mg) every 3 days; usual maintenance dose 1–2 g daily in 2 divided doses; max. 2.5 g daily in 2 divided doses

● By intravenous administration

Note If switching from oral therapy to intravenous therapy give current oral daily dose by intravenous injection or intermittent intravenous infusion in 2–4 divided doses, or by continuous intravenous infusion

Neonate by intravenous injection 10 mg/kg twice daily

Child 1 month–12 years initially 10 mg/kg by intravenous injection, followed by continuous intravenous infusion, or by intermittent intravenous infusion or intravenous injection in 2–4 divided doses up to usual range 20–40 mg/kg daily (doses above 40 mg/kg daily monitor clinical chemistry and haematological parameters)

Child 12–18 years initially 10 mg/kg by intravenous injection, followed by continuous intravenous infusion, or by intermittent intravenous infusion or intravenous injection in 2–4 divided doses up to max. 2.5 g daily; usual range 1–2 g daily (20–30 mg/kg daily)

Administration for rectal administration, sodium valproate oral solution may be given rectally and retained for 15 minutes (may require dilution with water to prevent rapid expulsion).

For intravenous injection, may be diluted in Glucose 5% or Sodium Chloride 0.9% and given over 3–5 minutes.

For intravenous infusion, dilute injection solution with Glucose 5% or Sodium Chloride 0.9%

▲ Oral

Sodium Valproate (Non-proprietary) PoM

Tablets (crushable), scored, sodium valproate 100 mg, net price 100-tab pack = £5.60. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Tablets, e/c, sodium valproate 200 mg, net price 100-tab pack = £4.00; 500 mg, 100-tab pack = £7.64. Label: 5, 8, 25, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Oral solution, sodium valproate 200 mg/5 mL, net price 300 mL = £9.33. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Note Patients may need to be maintained on a specific manufacturer's branded or generic oral sodium valproate product, see MHRA/CHM advice, p. 216

Epilim[®] (Sanofi-Aventis) PoM

Tablets (crushable), scored, sodium valproate 100 mg, net price 100-tab pack = £5.60. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Tablets, e/c, lilac, sodium valproate 200 mg, net price 100-tab pack = £7.70; 500 mg, 100-tab pack = £19.25. Label: 5, 8, 25, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Liquid, red, sugar-free, sodium valproate 200 mg/5 mL, net price 300-mL pack = £7.78. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Syrup, red, sodium valproate 200 mg/5 mL, net price 300-mL pack = £9.33. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Note May be diluted, preferably in Syrup BP; use within 14 days

Note Patients may need to be maintained on a specific manufacturer's branded or generic oral sodium valproate product, see MHRA/CHM advice, p. 216

▲ Modified release

Epilim Chrono[®] (Sanofi-Aventis) PoM

Tablets, m/r, lilac, sodium valproate 200 mg (as sodium valproate and valproic acid), net price 100-tab pack = £11.65; 300 mg, 100-tab pack = £17.47; 500 mg, 100-tab pack = £29.10. Label: 8, 21, 25, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Dose

Epilepsy

● By mouth

Child body-weight over 20 kg as above, total daily dose given in 1–2 divided doses

Note Patients may need to be maintained on a specific manufacturer's branded or generic oral sodium valproate product, see MHRA/CHM advice, p. 216

Epilim Chronosphere[®] (Sanofi-Aventis) PoM

Granules, m/r, sodium valproate 50 mg (as sodium valproate and valproic acid), net price 30-sachet pack = £30.00; 100 mg, 30-sachet pack = £30.00; 250 mg, 30-sachet pack = £30.00; 500 mg, 30-sachet pack = £30.00; 750 mg, 30-sachet pack = £30.00; 1 g, 30-sachet pack = £30.00. Label: 8, 21, 25, counselling, administration, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Dose

Epilepsy

● By mouth

Child as above to the nearest whole 50-mg sachet; total daily dose given in 1–2 divided doses

Counselling Granules may be mixed with soft food or drink that is cold or at room temperature and swallowed immediately without chewing

Note Patients may need to be maintained on a specific manufacturer's branded or generic oral sodium valproate product, see MHRA/CHM advice, p. 216

Episenta[®] (Desitin) PoM

Capsules, enclosing m/r granules, sodium valproate 150 mg, net price 100-cap pack = £7.00; 300 mg, 100-cap pack = £13.00. Label: 8, 21, 25, counselling, administration, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Dose

Epilepsy

● By mouth

Child as above, total daily dose given in 1–2 divided doses

Counselling Contents of capsule may be mixed with soft food or drink that is cold or at room temperature and swallowed immediately without chewing

Granules, m/r, sodium valproate 500 mg, net price 100-sachet pack = £21.00; 1 g, 100-sachet pack = £41.00. Label: 8, 21, 25, counselling, administration, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Dose**Epilepsy**● **By mouth**

Child as above, total daily dose given in 1–2 divided doses

Counselling Granules may be mixed with soft food or drink that is cold or at room temperature and swallowed immediately without chewing

Note Patients may need to be maintained on a specific manufacturer's branded or generic oral sodium valproate product, see MHRA/CHM advice, p. 216

Epival® (Chanelle Medical) (PoM)

Tablets, m/r, scored, sodium valproate 300 mg, net price 100-tab pack = £12.13; 500 mg 100-tab pack = £20.21. Label: 8, 21, 25, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Dose**Epilepsy**● **By mouth**

Child body-weight over 20 kg as above, total daily dose given in 1–2 divided doses

Counselling Tablets may be halved but not crushed or chewed

Note Patients may need to be maintained on a specific manufacturer's branded or generic oral sodium valproate product, see MHRA/CHM advice, p. 216

■ **Parenteral****Sodium Valproate** (Non-proprietary) (PoM)

Injection, sodium valproate 100 mg/mL, net price 3-mL amp = £7.00; 4-mL amp = £11.58

Brands include *Episenta®*

Epilim® Intravenous (Sanofi-Aventis) (PoM)

Injection, powder for reconstitution, sodium valproate, net price 400-mg vial (with 4-mL amp water for injections) = £13.32

■ **Valproic acid****Convulx®** (Pharmacia) (PoM)

Capsules, e/c, valproic acid 150 mg, net price 100-cap pack = £3.68; 300 mg, 100-cap pack = £7.35; 500 mg, 100-cap pack = £12.25. Label: 8, 21, 25, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Dose**Epilepsy**● **By mouth**

Child as for sodium valproate, total daily dose given in 2–4 divided doses

Equivalence to Sodium valproate Manufacturer advises that *Convulx®* has a 1:1 dose relationship with products containing sodium valproate, but nevertheless care is needed in making changes

Note Patients may need to be maintained on a specific manufacturer's branded or generic oral valproic acid product, see MHRA/CHM advice, p. 216

Vigabatrin

Vigabatrin can be prescribed in combination with other antiepileptic treatment for focal epilepsy with or without secondary generalisation. It should not be prescribed unless all other appropriate drug combinations are ineffective or have not been tolerated, and it should be initiated and supervised by an appropriate specialist. Vigabatrin can be prescribed as monotherapy in the management of infantile spasms in West's syndrome. Vigabatrin may worsen absence, myoclonic, tonic and atonic seizures.

About one-third of those treated with vigabatrin have suffered visual field defects; counselling and **careful monitoring** for this side-effect are required (see also Visual Field Defects under Cautions below). Vigabatrin has prominent behavioural side-effects in some children.

VIGABATRIN

Cautions closely monitor neurological function; avoid sudden withdrawal; history of psychosis, depression, or behavioural problems; absence seizures (may be exacerbated); **interactions**: see p. 217 and Appendix 1 (vigabatrin)

Visual field defects Vigabatrin is associated with visual field defects. The onset of symptoms varies from 1 month to several years after starting. In most cases, visual field defects have persisted despite discontinuation, and further deterioration after discontinuation cannot be excluded. Product literature advises visual field testing before treatment and at 6-month intervals. Children and their carers should be warned to report any new visual symptoms that develop and those with symptoms should be referred for an urgent ophthalmological opinion. Gradual withdrawal of vigabatrin should be considered.

Contra-indications visual field defects

Renal impairment consider reduced dose or increased dose interval if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²

Pregnancy see Pregnancy, p. 218

Breast-feeding present in milk—manufacturer advises avoid; see also Breast-feeding, p. 218

Side-effects nausea, abdominal pain; oedema; drowsiness (*rarely* encephalopathic symptoms including marked sedation, stupor, and confusion with non-specific slow wave EEG—reduce dose or withdraw), fatigue, excitation, agitation, dizziness, headache, nervousness, depression, aggression, irritability, paranoia, impaired concentration, impaired memory, tremor, paraesthesia, speech disorder, weight gain; visual field defects (see under Cautions); blurred vision, nystagmus, diplopia; *less commonly* ataxia, psychosis, mania, and rash; occasional increase in seizure frequency (especially if myoclonic); *rarely* suicidal ideation and retinal disorders (including peripheral retinal neuropathy); *very rarely* hepatitis, optic neuritis and optic atrophy; *also reported* movement disorders in infantile spasms

Indications and dose

Adjunctive treatment of focal seizures with or without secondary generalisation not satisfactorily controlled with other antiepileptics

● **By mouth**

Neonate initially 15–20 mg/kg twice daily increased over 2–3 weeks to usual maintenance dose 30–40 mg/kg twice daily; max. 75 mg/kg twice daily

Child 1 month–2 years initially 15–20 mg/kg twice daily increased over 2–3 weeks to usual maintenance dose 30–40 mg/kg twice daily; max. 75 mg/kg twice daily

Child 2–12 years initially 15–20 mg/kg (max. 250 mg) twice daily increased over 2–3 weeks to usual maintenance dose 30–40 mg/kg (max. 1.5 g) twice daily

Child 12–18 years initially 250 mg twice daily increased over 2–3 weeks to usual maintenance dose 1–1.5 g twice daily

Administration Tablets may be crushed and dispersed in liquid

- By rectum

Child 1 month–18 years dose as for oral therapy, see above

Administration dissolve contents of sachet in small amount of water and administer rectally

Infantile spasms as monotherapy

- By mouth

Neonate initially 15–25 mg/kg twice daily adjusted according to response over 7 days to usual maintenance dose 40–50 mg/kg twice daily; max. 75 mg/kg twice daily

Child 1 month–2 years initially 15–25 mg/kg twice daily adjusted according to response over 7 days to usual maintenance dose 40–50 mg/kg twice daily; max. 75 mg/kg twice daily

Sabril® (Sanofi-Aventis) (POM)

Tablets, f/c, scored, vigabatrin 500 mg, net price 100-tab pack = £37.01. Label: 3, 8, counselling, driving (see notes above)

Powder, sugar-free, vigabatrin 500 mg/sachet. Net price 50-sachet pack = £20.50. Label: 3, 8, 13, counselling, driving (see notes above)

Note The contents of a sachet should be dissolved in water or a soft drink immediately before taking

Zonisamide

Zonisamide can be used as an adjunctive treatment for refractory focal seizures with or without secondary generalisation in children and adolescents aged 6 years and above. It can also be used under the supervision of a specialist for refractory absence and myoclonic seizures [unlicensed indications].

ZONISAMIDE

Cautions avoid overheating and ensure adequate hydration especially during strenuous activity or if in warm environment (fatal cases of heat stroke reported, also see Counselling below); risk factors for renal stone formation (particularly predisposition to nephrolithiasis); concomitant use of drugs that increase risk of nephrolithiasis; metabolic acidosis—monitor serum bicarbonate concentration in all children (consider dose reduction or discontinuation if metabolic acidosis develops); avoid abrupt withdrawal (consult product literature for recommended withdrawal regimens); low body-weight or poor appetite—monitor weight throughout treatment (fatal cases of weight loss reported); **interactions:** see p. 217 and Appendix 1 (zonisamide)

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history (see also MHRA/CHM advice, p. 216)

Contra-indications hypersensitivity to sulfonamides; concomitant use of drugs that increase risk of hyperthermia or metabolic acidosis

Hepatic impairment initially increase dose at 2-week intervals if mild or moderate impairment; avoid in severe impairment

Renal impairment initially increase dose at 2-week intervals; discontinue if renal function deteriorates

Pregnancy manufacturer advises women of child-bearing potential should use adequate contraception during treatment and for 4 weeks after last dose; also see Pregnancy, p. 218

Breast-feeding manufacturer advises avoid for 4 weeks after last dose; see also Breast-feeding, p. 218

Side-effects nausea, diarrhoea, abdominal pain, constipation, dyspepsia, anorexia, weight loss, peripheral oedema, drowsiness, dizziness, confusion, agitation, irritability, depression, psychosis, ataxia, speech disorder, impaired memory and attention, fatigue, nystagmus, paraesthesia, tremor, pyrexia, insomnia, diplopia, ecchymosis, alopecia, pruritus, rash (consider withdrawal); *less commonly* vomiting, cholelithiasis, cholecystitis, aggression, suicidal ideation, seizures, pneumonia, urinary tract infection, urinary calculus, hypokalaemia; *very rarely* hepatitis, pancreatitis, aspiration, dyspnoea, hallucinations, amnesia, coma, myasthenic syndrome, neuroleptic malignant syndrome, heat stroke, hydronephrosis, renal failure, metabolic acidosis, renal tubular acidosis, blood disorders, rhabdomyolysis, impaired sweating, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Indications and dose

Adjunctive treatment of refractory focal seizures with or without secondary generalisation

- By mouth

Child 6–18 years initially 1 mg/kg once daily for 7 days, then increased by 1 mg/kg every 7 days; usual maintenance, body-weight 20–55 kg, 6–8 mg/kg once daily (max. 500 mg once daily), body-weight over 55 kg, 300–500 mg once daily

Note Increase dose at 2-week intervals in patients who are not receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4

Counselling Children and their carers should be made aware of how to prevent and recognise overheating and dehydration

Zonegran® (Eisai) (POM)

Capsules, zonisamide 25 mg (white), net price 14-cap pack = £8.82; 50 mg (white/grey), 56-cap pack = £47.04; 100 mg (white/red), 56-cap pack = £62.72. Label: 3, 8, 10, counselling, overheating (see above)

Note Patients may need to be maintained on a specific manufacturer's branded or generic zonisamide product, see MHRA/CHM advice, p. 216

Benzodiazepines

Clobazam may be used as adjunctive therapy in the treatment of generalised tonic-clonic and refractory focal seizures. It may be prescribed under the care of a specialist for refractory absence and myoclonic seizures. **Clonazepam** may be prescribed by a specialist for refractory absence and myoclonic seizures, but its sedative side-effects may be prominent. The effectiveness of clobazam and clonazepam may decrease significantly after weeks or months of continuous therapy.

Hepatic impairment Benzodiazepines can precipitate coma if used in hepatic impairment. Start with smaller initial doses or reduce dose; avoid in severe impairment.

Renal impairment Children with renal impairment have increased cerebral sensitivity to benzodiazepines; start with small doses in severe impairment.

Pregnancy There is a risk of neonatal withdrawal symptoms when benzodiazepines are used during pregnancy. Avoid regular use and use only if there is a clear indication such as seizure control. High doses administered during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

Breast-feeding Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

CLOBAZAM

Cautions see Diazepam, section 4.8.2

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history (see also MHRA/CHM advice, p. 216)

Contra-indications see Diazepam, section 4.8.2

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see Diazepam, section 4.8.2

Licensed use not licensed for use in children under 6 years; not licensed as monotherapy

Indications and dose

Adjunctive therapy for epilepsy, monotherapy under specialist supervision for catamenial (menstruation) seizures (usually for 7–10 days each month, just before and during menstruation), cluster seizures

• By mouth

Child 1 month–6 years initially 125 micrograms/kg twice daily, increased if necessary every 5 days to usual maintenance dose of 250 micrograms/kg twice daily; max. 500 micrograms/kg twice daily, not exceeding 15 mg twice daily

Child 6–18 years initially 5 mg daily, increased if necessary every 5 days to usual maintenance dose of 0.3–1 mg/kg daily; max. 60 mg daily; daily doses of up to 30 mg may be given as a single dose at bedtime, higher doses should be divided

¹Clobazam (Non-proprietary) [CD4-1]

Tablets, clobazam 10 mg. Net price 30-tab pack = £2.70. Label: 2 or 19, 8, counselling, driving (see notes above)

Brands include *Fristum*® JMS

Tablets, clobazam 5 mg available on a named patient basis

Oral suspension, clobazam 5 mg/5 mL, net price 150 mL = £115.61; 10 mg/5 mL, net price 150 mL = £120.25. Label: 2, or 19, 8, counselling, driving, (see notes above)

Brands include *Tapclab*®

Note Patients may need to be maintained on a specific manufacturer's branded or generic clobazam product, see MHRA/CHM advice, p. 216

1. JMS except for epilepsy and endorsed 'SLS'

CLONAZEPAM

Cautions see notes above; respiratory disease, airways obstruction; spinal or cerebellar ataxia; brain damage; myasthenia gravis (avoid if unstable); history of alcohol or drug abuse, depression or suicidal ideation; debilitated patients; avoid sudden withdrawal; acute porphyria (section 9.8.2); **interactions:** see p. 217 and Appendix 1 (anxiolytics and hypnotics) **Driving** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history (see also MHRA/CHM advice, p. 216)

Contra-indications respiratory depression; acute pulmonary insufficiency; sleep apnoea syndrome; marked neuromuscular respiratory weakness including unstable myasthenia gravis; coma; current alcohol or drug abuse

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects drowsiness, fatigue, dizziness, muscle hypotonia, coordination disturbances; also poor concentration, restlessness, confusion, amnesia, dependence, withdrawal symptoms; salivary or bronchial hypersecretion in infants and small children; nystagmus; rarely gastro-intestinal symptoms, respiratory depression, headache, paradoxical effects including aggression and anxiety, sexual dysfunction, urinary incontinence, urticaria, pruritus, reversible hair loss, skin pigmentation changes; dysarthria, and visual disturbances on long-term treatment; blood disorders reported; *very rarely* increase in seizure frequency; **overdose:** see Emergency Treatment of Poisoning, p. 29

Indications and dose

All forms of epilepsy

• By mouth

Child 1 month–1 year initially 250 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 0.5–1 mg at night (may be given in 3 divided doses if necessary)

Child 1–5 years initially 250 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 1–3 mg at night (may be given in 3 divided doses if necessary)

Child 5–12 years initially 500 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 3–6 mg at night (may be given in 3 divided doses if necessary)

Child 12–18 years initially 1 mg at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 4–8 mg at night (may be given in 3–4 divided doses if necessary)

Note Clonazepam doses in BNFC may differ from those in product literature

Clonazepam (Non-proprietary) [CD4-1]

Tablets, clonazepam 500 micrograms, net price 100-tab pack = £3.49; 2 mg, 100 tab-pack = £4.87. Label: 2, 8, counselling, driving (see notes above)

Note Patients may need to be maintained on a specific manufacturer's branded or generic oral clonazepam product, see MHRA/CHM advice, p. 216

Rivotril® (Roche) [CD4-1]

Tablets, scored, clonazepam 500 micrograms (beige), net price 100-tab pack = £3.69; 2 mg (white), 100-tab pack = £4.93. Label: 2, 8, counselling, driving (see notes above)

Liquid, clonazepam 500 micrograms/5 mL; 2 mg/5 mL; 2.5 mg/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Note Patients may need to be maintained on a specific manufacturer's branded or generic oral clonazepam product, see MHRA/CHM advice, p. 216

Other drugs

Acetazolamide (section 11.6), a carbonic anhydrase inhibitor, has a specific role in treating epilepsy associated with menstruation.

Piracetam is used as adjunctive treatment for cortical myoclonus.

4.8.2 Drugs used in status epilepticus

Convulsive status epilepticus Immediate measures to manage status epilepticus include positioning the child to avoid injury, supporting respiration including the provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia. **Pyridoxine** (section 9.6.2) should be administered if the status epilepticus is caused by pyridoxine deficiency.

Seizures lasting 5 minutes should be treated urgently with buccal **midazolam** or intravenous **lorazepam** (repeated once after 10 minutes if seizures recur or fail to respond). Intravenous **diazepam** is effective but it carries a high risk of venous thrombophlebitis (reduced by using an emulsion formulation of diazepam injection). Patients should be monitored for respiratory depression and hypotension.

Important

If, after initial treatment with benzodiazepines, seizures recur or fail to respond 25 minutes after onset, phenytoin sodium should be used, or if the child is on regular phenytoin, give phenobarbital intravenously over 5 minutes; the paediatric intensive care unit should be contacted. Paraldehyde can be given after starting phenytoin infusion.

If these measures fail to control seizures 45 minutes after onset, anaesthesia with thiopental (section 15.1.1) should be instituted with full intensive care support.

Phenytoin sodium can be given by intravenous infusion over 20 minutes, followed by the maintenance dosage if appropriate; monitor ECG and blood pressure, and reduce rate of administration if bradycardia or hypotension occurs. Intramuscular phenytoin should not be used (absorption is slow and erratic).

Paraldehyde given rectally causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

For neonatal seizures, see p. 219.

Non-convulsive status epilepticus The urgency to treat non-convulsive status epilepticus depends on the severity of the child's condition. If there is incom-

plete loss of awareness, oral antiepileptic therapy should be restarted or continued. Children who fail to respond to oral antiepileptic therapy or have complete lack of awareness can be treated in the same way as convulsive status epilepticus, although anaesthesia is rarely needed.

DIAZEPAM

Cautions respiratory disease; muscle weakness and myasthenia gravis; history of drug or alcohol dependence; organic brain changes; personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence; avoid prolonged use (and abrupt withdrawal thereafter); when given parenterally, close observation required until full recovery from sedation; when given intravenously, facilities for reversing respiratory depression with mechanical ventilation must be immediately available (but see also notes above); **interactions:** Appendix 1 (anxiolytics and hypnotics) **Skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; sleep apnoea syndrome; phobic or obsessional states; hyperkinesia; avoid injections containing benzyl alcohol in neonates (see under preparations below)

Hepatic impairment see Benzodiazepines, section 4.8.1

Renal impairment see Benzodiazepines, section 4.8.1

Pregnancy see Benzodiazepines, section 4.8.1

Breast-feeding see Benzodiazepines, section 4.8.1

Side-effects drowsiness and lightheadedness the next day, confusion and ataxia, amnesia, dependence, paradoxical increase in aggression, muscle weakness; *occasionally:* dizziness, salivation changes, gynaecomastia, gastro-intestinal disturbances, visual disturbances, dysarthria, tremor, incontinence; *rarely* hypotension, apnoea, respiratory depression, headache, vertigo, changes in libido, urinary retention, blood disorders, jaundice, skin reactions; on intravenous injection, pain, thrombophlebitis; *also reported* irritability, delusions, excitement, restlessness, hallucinations, psychosis; **overdosage:** see Emergency Treatment of Poisoning, p. 29

Licensed use *Diazepam Desitin®*, *Diazepam Rectubes®*, and *Stesolid Rectal Tubes®* not licensed for use in children under 1 year

Indications and dose

Status epilepticus, febrile convulsions (section 4.8.3), convulsions caused by poisoning

- By intravenous injection over 3–5 minutes

Neonate 300–400 micrograms/kg repeated once after 10 minutes if necessary

Child 1 month–12 years 300–400 micrograms/kg (max. 10 mg) repeated once after 10 minutes if necessary

Child 12–18 years 10 mg repeated once after 10 minutes if necessary

- By rectum (as rectal solution)

Neonate 1.25–2.5 mg repeated once after 10 minutes if necessary

Child 1 month–2 years 5 mg repeated once after 10 minutes if necessary

Child 2–12 years 5–10 mg repeated once after 10 minutes if necessary

Child 12–18 years 10–20 mg repeated once after 10 minutes if necessary

Life-threatening acute drug-induced dystonic reactions (section 4.9.2)

- By intravenous injection over 3–5 minutes

Child 1 month–12 years 100 micrograms/kg repeat doses as necessary

Child 12–18 years 5–10 mg repeat doses as necessary

Muscle spasm section 10.2.2

Diazepam (Non-proprietary) (CD4-1)

Injection (solution), diazepam 5 mg/mL, net price 2-mL amp = 45p

Excipients include benzyl alcohol (avoid in neonates unless there is no safer alternative available, see Excipients, p. 2), ethanol, propylene glycol

Injection (emulsion), diazepam 5 mg/mL (0.5%), net price 2-mL amp = 91p

Brands include *Diazemuls*®

Rectal tubes (= rectal solution), diazepam 2 mg/mL, net price 1.25-mL (2.5-mg) tube = £1.13, 2.5-mL (5-mg) tube = £1.09; 4 mg/mL, 2.5-mL (10-mg) tube = £1.37

Brands include *Diazepam Desitin*®, *Diazepam Rectubes*®, *Stesolid*®

FOSPHENYTOIN SODIUM

Note Fosphenytoin is a pro-drug of phenytoin

Cautions see Phenytoin Sodium; resuscitation facilities must be available; **interactions:** see p. 217 and Appendix 1 (phenytoin)

Contra-indications see Phenytoin Sodium

Hepatic impairment consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus)

Renal impairment consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus)

Pregnancy see Phenytoin (section 4.8.1) and Pregnancy, p. 218

Breast-feeding see Phenytoin (section 4.8.1)

Side-effects see Phenytoin Sodium; also dry mouth, taste disturbance, vasodilatation, asthenia, dysarthria, euphoria, incoordination, chills, visual disturbances, tinnitus, pruritus, ecchymosis; *less commonly* hypoaesthesia, increased or decreased reflexes, stupor, muscle weakness, muscle spasm, pain, hypoaecusis; *also reported* extrapyramidal disorder, twitching, confusion, hyperglycaemia

Important Intravenous infusion of fosphenytoin has been associated with severe cardiovascular reactions including asystole, ventricular fibrillation, and cardiac arrest. Hypotension, bradycardia, and heart block have also been reported. The following are recommended:

- monitor heart rate, blood pressure, and respiratory function for duration of infusion;
- observe patient for at least 30 minutes after infusion;
- if hypotension occurs, reduce infusion rate or discontinue;
- reduce dose or infusion rate in renal or hepatic impairment.

Indications and dose

Expressed as **phenytoin sodium equivalent (PE)**; fosphenytoin sodium 1.5 mg \equiv phenytoin sodium 1 mg

Status epilepticus

- By intravenous infusion (at a rate of 2–3 mg(PE)/kg/minute, max. 150 mg(PE)/minute)

Child 5–18 years initially 20 mg(PE)/kg, then (at a rate of 1–2 mg(PE)/kg/minute, max. 100 mg(PE)/minute) 4–5 mg(PE)/kg; total daily dose may be given in 1–4 divided doses; adjusted according to response and trough plasma-phenytoin concentration

Prophylaxis or treatment of seizures associated with neurosurgery or head injury

- By intravenous infusion (at a rate of 1–2 mg(PE)/kg/minute, max. 100 mg(PE)/minute)

Child 5–18 years initially 10–15 mg(PE)/kg then 4–5 mg(PE)/kg daily; total daily dose may be given in 1–4 divided doses; adjusted according to response and trough plasma-phenytoin concentration

Temporary substitution for oral phenytoin

- By intravenous infusion (at a rate of 1–2 mg(PE)/kg/minute, max. 100 mg (PE)/minute)

Child 5–18 years same dose and dosing frequency as oral phenytoin therapy

Note Fosphenytoin sodium doses in BNFC may differ from those in product literature

Note

Prescriptions for fosphenytoin sodium should state the dose in terms of phenytoin sodium equivalent (PE)

Administration for *intermittent intravenous infusion*, dilute to a concentration of 1.5–25 mg (PE)/mL with Glucose 5% or Sodium Chloride 0.9%

Pro-Epanutin® (Pfizer) (PoM)

Injection, fosphenytoin sodium 75 mg/mL (equivalent to phenytoin sodium 50 mg/mL), net price 10-mL vial = £40.00

Electrolytes phosphate 3.7 micromol/mg fosphenytoin sodium (phosphate 5.6 micromol/mg phenytoin sodium)

LORAZEPAM

Cautions see Diazepam; facilities for reversing respiratory depression with mechanical ventilation must be immediately available

Contra-indications see Diazepam

Hepatic impairment see Benzodiazepines, section 4.8.1

Renal impairment see Benzodiazepines, section 4.8.1

Pregnancy see Benzodiazepines, section 4.8.1

Breast-feeding see Benzodiazepines, section 4.8.1

Side-effects see Diazepam; hypotension and apnoea

Licensed use not licensed for use in febrile convulsions or convulsions caused by poisoning

Indications and dose**Status epilepticus, febrile convulsions (section 4.8.3), convulsions caused by poisoning**

● By slow intravenous injection

Neonate 100 micrograms/kg as a single dose, repeated once after 10 minutes if necessary

Child 1 month–12 years 100 micrograms/kg (max. 4 mg) as a single dose, repeated once after 10 minutes if necessary

Child 12–18 years 4 mg as a single dose, repeated once after 10 minutes if necessary

Peri-operative use

Section 15.1.4.1

Administration for *intravenous injection*, dilute with an equal volume of Sodium Chloride 0.9% (for neonates, dilute injection solution to a concentration of 100 micrograms/mL)

■ **Preparations**

Section 15.1.4.1

MIDAZOLAM

Cautions see Midazolam, section 15.1.4.1

Contra-indications see Midazolam, section 15.1.4.1

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe impairment

Renal impairment use with caution in chronic renal failure

Pregnancy see Midazolam, section 15.1.4.1 and Pregnancy, p. 218

Breast-feeding amount probably too small to be harmful after single doses

Side-effects see Midazolam, section 15.1.4.1

Licensed use oromucosal solution not licensed for use in children under 3 months; injection not licensed for use in status epilepticus or febrile convulsions

Indications and dose**Status epilepticus, febrile convulsions (section 4.8.3)**

● By buccal administration

Neonate 300 micrograms/kg, repeated once after 10 minutes if necessary

Child 1–3 months 300 micrograms/kg (max. 2.5 mg), repeated once after 10 minutes if necessary

Child 3 months–1 year 2.5 mg, repeated once after 10 minutes if necessary

Child 1–5 years 5 mg, repeated once after 10 minutes if necessary

Child 5–10 years 7.5 mg, repeated once after 10 minutes if necessary

Child 10–18 years 10 mg, repeated once after 10 minutes if necessary

● By intravenous administration

Neonate initially by *intravenous injection* 150–200 micrograms/kg followed by *continuous intravenous infusion* of 60 micrograms/kg/hour (increased by 60 micrograms/kg/hour every 15 minutes until seizure controlled); max. 300 micrograms/kg/hour

Child 1 month–18 years initially by *intravenous injection* 150–200 micrograms/kg followed by

continuous intravenous infusion of 60 micrograms/kg/hour (increased by 60 micrograms/kg/hour every 15 minutes until seizure controlled); max. 300 micrograms/kg/hour

Administration for *intravenous injection*, dilute with Glucose 5% or Sodium Chloride 0.9%; rapid intravenous injection (less than 2 minutes) may cause seizure-like myoclonus in preterm neonate
Neonatal intensive care, dilute 15 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 30 micrograms/kg/hour

Buccolam (ViroPharma) ▼ [CD3]

Oromucosal solution, midazolam (as hydrochloride) 5 mg/mL, net price 0.5-mL (2.5 mg) prefilled syringe = £20.50, 1-mL (5 mg) prefilled syringe = £21.38, 1.5-mL (7.5 mg) prefilled syringe = £22.25, 2-mL (10 mg) prefilled syringe = £22.88. Label: 2, counseling, administration

Note Other unlicensed formulations are also available and may have different doses—refer to product literature

■ **Parenteral preparations**

Section 15.1.4

PARALDEHYDE

Cautions bronchopulmonary disease; **interactions:** Appendix 1 (paraldehyde)

Contra-indications gastric disorders; rectal administration in colitis

Hepatic impairment use with caution

Pregnancy avoid unless essential—crosses placenta

Breast-feeding avoid unless essential—present in milk

Side-effects rash

Licensed use not licensed for use in children as an enema

Indications and dose**Status epilepticus**

● By rectum

See preparation

Paraldehyde in olive oil (Non-proprietary) [PoM]

Enema, premixed solution of paraldehyde in olive oil in equal volumes, available from 'special-order' manufacturers or specialist importing companies, p. 840

Dose

Status epilepticus

● By rectum

Neonate 0.8 mL/kg as a single dose

Child 1 month–18 years 0.8 mL/kg (max. 20 mL) as a single dose

PHENOBARBITAL SODIUM

(Phenobarbitone sodium)

Cautions see Phenobarbital, section 4.8.1; **interactions:** see p. 217 and Appendix 1 (phenobarbital)

Hepatic impairment see Phenobarbital, section 4.8.1

Renal impairment see Phenobarbital, section 4.8.1

Pregnancy see Pregnancy, p. 218

Breast-feeding see Phenobarbital, section 4.8.1

Side-effects see Phenobarbital, section 4.8.1

Indications and dose**Status epilepticus**

- By slow intravenous injection (no faster than 1 mg/kg/minute)

Neonate initially 20 mg/kg then 2.5–5 mg/kg once or twice daily

Child 1 month–12 years initially 20 mg/kg then 2.5–5 mg/kg once or twice daily

Child 12–18 years initially 20 mg/kg (max. 1 g) then 300 mg twice daily

Other forms of epilepsy section 4.8.1

Administration for intravenous injection, dilute to a concentration of 20 mg/mL with Water for Injections

Phenobarbital (Non-proprietary) (Cb3)

Injection, phenobarbital sodium 15 mg/mL, net price 1-mL amp = £1.97; 30 mg/mL, 1-mL amp = £6.66; 60 mg/mL, 1-mL amp = £7.08; 200 mg/mL, 1-mL amp = £5.77

Excipients include propylene glycol (see Excipients, p. 2)

Note Must be diluted before intravenous administration (see Administration)

PHENYTOIN SODIUM

Cautions see notes above; respiratory depression; hypotension and heart failure; resuscitation facilities must be available; injection solutions alkaline (irritant to tissues); see also p. 227; **interactions**: see p. 217 and Appendix 1 (phenytoin)

Contra-indications sinus bradycardia, sino-atrial block, and second- and third-degree heart block; Stokes-Adams syndrome; acute porphyria (section 9.8.2)

Hepatic impairment see Phenytoin, section 4.8.1

Pregnancy see Phenytoin, section 4.8.1 and Pregnancy, p. 218

Breast-feeding see Phenytoin, section 4.8.1

Side-effects intravenous injection may cause cardiovascular and CNS depression (particularly if injection too rapid) with arrhythmias, hypotension, and cardiovascular collapse; alterations in respiratory function (including respiratory arrest); also reported tonic seizures, purple glove syndrome; see also p. 227

Indications and dose

Status epilepticus, acute symptomatic seizures associated with trauma or neurosurgery

- By slow intravenous injection or infusion (with blood-pressure and ECG monitoring)

Neonate initially 20 mg/kg as a loading dose then 2.5–5 mg/kg twice daily

Child 1 month–12 years initially 20 mg/kg as a loading dose then 2.5–5 mg/kg twice daily

Child 12–18 years initially 20 mg/kg as a loading dose then up to 100 mg 3–4 times daily

Other forms of epilepsy section 4.8.1

Note Phenytoin sodium doses in BNFC may differ from those in product literature

Administration before and after administration flush intravenous line with Sodium Chloride 0.9%.

For intravenous injection, give into a large vein at rate not exceeding 1 mg/kg/minute (max. 50 mg/minute).

For intravenous infusion, dilute to a concentration not exceeding 10 mg/mL with Sodium Chloride 0.9% and give into a large vein through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute); complete administration within 1 hour of preparation

Phenytoin (Non-proprietary) (PoM)

Injection, phenytoin sodium 50 mg/mL with propylene glycol 40% and alcohol 10% in water for injections, net price 5-mL amp = £2.91

Epanutin® Ready-Mixed Parenteral (Pfizer) (PoM)

Injection, phenytoin sodium 50 mg/mL with propylene glycol 40% and alcohol 10% in water for injections. Net price 5-mL amp = £4.88

4.8.3 Febrile convulsions

Brief febrile convulsions need no specific treatment; antipyretic medication (e.g. paracetamol, section 4.7.1) is commonly used to reduce fever and prevent further convulsions but evidence to support this practice is lacking. Prolonged febrile convulsions (those lasting 5 minutes or longer), or recurrent febrile convulsions without recovery, must be treated actively (as for convulsive status epilepticus section 4.8.2).

Long-term anticonvulsant prophylaxis for febrile convulsions is rarely indicated.

4.9 Drugs used in dystonias and related disorders

4.9.1 Dopaminergic drugs used in dystonias

4.9.2 Antimuscarinic drugs used in dystonias

4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders

Dystonias may result from conditions such as cerebral palsy or may be related to a deficiency of the neurotransmitter dopamine as in Segawa syndrome.

4.9.1 Dopaminergic drugs used in dystonias

Levodopa, the amino-acid precursor of dopamine, acts by replenishing depleted striatal dopamine. It is given with an extracerebral dopa-decarboxylase inhibitor, which reduces the peripheral conversion of levodopa to dopamine, thereby limiting side-effects such as nausea, vomiting, and cardiovascular effects; additionally, effective brain-dopamine concentrations are achieved with lower doses of levodopa. The extracerebral dopa-decarboxylase inhibitor most commonly used in children is carbidopa (in co-careldopa).

Levodopa therapy should be initiated at a low dose and increased in small steps; the final dose should be as low as possible. Intervals between doses should be chosen to suit the needs of the individual child.

In severe dystonias related to cerebral palsy, improvement can be expected within 2 weeks. Children with Segawa syndrome are particularly sensitive to levodopa; they may even become symptom free on small

doses. Levodopa also has a role in treating metabolic disorders such as defects in tetrahydrobiopterin synthesis and dihydrobiopterin reductase deficiency. For the use of tetrahydrobiopterin in metabolic disorders see section 9.4.1.

Children may experience nausea within 2 hours of taking a dose; nausea and vomiting with co-careldopa is rarely dose-limiting.

In dystonic cerebral palsy, treatment with larger doses of levodopa is associated with the development of potentially troublesome motor complications (including response fluctuations and dyskinesias). Response fluctuations are characterised by large variations in motor performance, with normal function during the 'on' period, and weakness and restricted mobility during the 'off' period.

Sudden onset of sleep

Excessive daytime sleepiness and sudden onset of sleep can occur with co-careldopa.

Children starting treatment with these drugs, and their carers, should be warned of the risk and of the need to exercise caution when performing skilled tasks e.g. driving or operating machinery. Children who have experienced excessive sedation or sudden onset of sleep should refrain from performing skilled tasks until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Children, and their carers, should be counselled on improving sleep behaviour.

CO-CARELDOPA

A mixture of carbidopa and levodopa; the proportions are expressed in the form x/y where x and y are the strengths in milligrams of carbidopa and levodopa respectively

Cautions see also notes above; pulmonary disease, peptic ulceration, cardiovascular disease (including history of myocardial infarction with residual arrhythmia), diabetes mellitus, osteomalacia, susceptibility to angle-closure glaucoma, history of skin melanoma (risk of activation), psychiatric illness (avoid if severe and discontinue if deterioration); warn children and carers about excessive drowsiness (see notes above); in prolonged therapy, psychiatric, hepatic, haematological, renal, and cardiovascular monitoring is advisable; warn patients to resume normal activities gradually; avoid abrupt withdrawal; interactions: Appendix 1 (levodopa)

Pregnancy use with caution—toxicity in *animal studies*

Breast-feeding may suppress lactation; present in milk—avoid

Side-effects see also notes above; anorexia, nausea and vomiting, insomnia, agitation, postural hypotension (rarely labile hypertension), dizziness, tachycardia, arrhythmias, reddish discoloration of urine and other body fluids; rarely hypersensitivity; very rarely angle-closure glaucoma; abnormal involuntary movements and psychiatric symptoms which include hypomania and psychosis may be dose-limiting; depression, drowsiness, headache, flushing, sweating, gastro-intestinal bleeding, peripheral neuropathy, taste disturbance, pruritus, rash, and liver enzyme changes also reported; syndrome resembling neuroleptic malignant syndrome reported on withdrawal

Licensed use not licensed for use in children

Indications and dose

Dopamine-sensitive dystonias including Segawa syndrome and dystonias related to cerebral palsy

• By mouth, expressed as levodopa

Child 3 months–18 years initially 250 micrograms/kg 2–3 times daily of a preparation containing 1:4 carbidopa:levodopa, increased according to response every 2–3 days to max. 1 mg/kg three times daily

Treatment of defects in tetrahydrobiopterin synthesis and dihydrobiopterin reductase deficiency

• By mouth, expressed as levodopa

Neonate initially 250–500 micrograms/kg 4 times daily of a preparation containing 1:4 carbidopa:levodopa, increased according to response every 4–5 days to maintenance dose of 2.5–3 mg/kg 4 times daily; at higher doses consider preparation containing 1:10 carbidopa:levodopa; review regularly (every 3–6 months)

Child 1 month–18 years initially 250–500 micrograms/kg 4 times daily of a preparation containing 1:4 carbidopa:levodopa, increased according to response every 4–5 days to maintenance dose of 2.5–3 mg/kg 4 times daily; at higher doses consider preparation containing 1:10 carbidopa:levodopa; review regularly (every 3–6 months in early childhood)

Co-careldopa (Non-proprietary) (PoM)

Tablets, co-careldopa 10/100 (carbidopa 10 mg (anhydrous), levodopa 100 mg), net price 100-tab pack = £8.26. Label: 14, counselling, skilled tasks, see notes above

Tablets, co-careldopa 25/100 (carbidopa 25 mg (anhydrous), levodopa 100 mg), net price 100-tab pack = £25.95. Label: 14, counselling, skilled tasks, see notes above

Tablets, co-careldopa 25/250 (carbidopa 25 mg (anhydrous), levodopa 250 mg), net price 100-tab pack = £34.25. Label: 14, counselling, skilled tasks, see notes above

Sinemet® (MSD) (PoM)

Sinemet® 12.5 mg/50 mg tablets, yellow, scored, co-careldopa 12.5/50 (carbidopa 12.5 mg (anhydrous), levodopa 50 mg), net price 90-tab pack = £6.28. Label: 14, counselling, skilled tasks, see notes above

Note 2 tablets *Sinemet*® 12.5 mg/50 mg = 1 tablet *Sinemet*® Plus 25 mg/100 mg

Sinemet® 10 mg/100 mg tablets, blue, scored, co-careldopa 10/100 (carbidopa 10 mg (anhydrous), levodopa 100 mg), net price 90-tab pack = £6.57. Label: 14, counselling, skilled tasks, see notes above

Sinemet® Plus 25 mg/100 mg tablets, yellow, scored, co-careldopa 25/100 (carbidopa 25 mg (anhydrous), levodopa 100 mg), net price 90-tab pack = £9.66. Label: 14, counselling, skilled tasks, see notes above

Sinemet® 25 mg/250 mg tablets, blue, scored, co-careldopa 25/250 (carbidopa 25 mg (anhydrous), levodopa 250 mg), net price 90-tab pack = £13.72. Label: 14, counselling, skilled tasks, see notes above

4.9.2 Antimuscarinic drugs used in dystonias

The antimuscarinic drugs **procyclidine** and **trihexyphenidyl** reduce the symptoms of dystonias, including those induced by antipsychotic drugs; there is no justification for giving them routinely in the absence of dystonic symptoms. Tardive dyskinesia is not improved by antimuscarinic drugs and may be made worse.

There are no important differences between the antimuscarinic drugs, but some children tolerate one better than another.

Procyclidine can be given parenterally and is effective emergency treatment for acute drug-induced dystonic reactions.

If treatment with an antimuscarinic is ineffective, intravenous **diazepam** (p. 236) can be given for life-threatening acute drug-induced dystonic reactions.

Cautions Antimuscarinics should be used with caution in cardiovascular disease, hypertension, psychotic disorders, pyrexia, and in those susceptible to angle-closure glaucoma. Antimuscarinics should not be withdrawn abruptly in children taking long-term treatment. Antimuscarinics are liable to abuse. **Interactions:** Appendix 1 (Antimuscarinics).

Skilled tasks Antimuscarinics can affect performance of skilled tasks (e.g. driving).

Contra-indications Antimuscarinics should be avoided in gastro-intestinal obstruction and myasthenia gravis.

Hepatic and renal impairment Procyclidine and trihexyphenidyl should be used with caution in children with hepatic or renal impairment.

Side-effects Side-effects of antimuscarinics include constipation, dry mouth, nausea, vomiting, tachycardia, dizziness, anxiety, euphoria, hallucinations, impaired memory, anxiety, restlessness, urinary retention, blurred vision, and rash. Angle-closure glaucoma occurs very rarely.

PROCYCLIDINE HYDROCHLORIDE

Cautions see notes above; **interactions:** Appendix 1 (antimuscarinics)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy use only if potential benefit outweighs risk

Breast-feeding no information available

Side-effects see notes above; also gingivitis

Licensed use not licensed for use in children

Indications and dose

Dystonias

- By mouth

Child 7–12 years 1.25 mg 3 times daily

Child 12–18 years 2.5 mg 3 times daily

Acute dystonia

- By intramuscular or intravenous injection

Child under 2 years 0.5–2 mg as a single dose

Child 2–10 years 2–5 mg as a single dose

Child 10–18 years 5–10 mg (occasionally more than 10 mg)

Note Usually effective in 5–10 minutes but may need 30 minutes for relief

Procyclidine (Non-proprietary) (PoM)

Tablets, procyclidine hydrochloride 5 mg, net price 28-tab pack = £1.63. Counselling, driving

Arpicolin® (Rosemont) (PoM)

Syrup, sugar-free, procyclidine hydrochloride 2.5 mg/5 mL, net price 150 mL = £4.22; 5 mg/5 mL, 150 mL pack = £7.54. Counselling, driving

Kemadrin® (Aspen) (PoM)

Tablets, scored, procyclidine hydrochloride 5 mg, net price 100-tab pack = £4.72. Counselling, driving

Kemadrin® (Auden Mckenzie) (PoM)

Injection, procyclidine hydrochloride 5 mg/mL, net price 2-mL amp = £1.49

TRIHEXYPHENIDYL HYDROCHLORIDE (Benzhexol hydrochloride)

Cautions see notes above; **interactions:** Appendix 1 (antimuscarinics)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy use only if potential benefit outweighs risk

Breast-feeding avoid

Side-effects see notes above

Licensed use not licensed for use in children

Indications and dose

Dystonia

- By mouth

Child 3 months–18 years initially 1–2 mg daily in 1–2 divided doses, increased every 3–7 days by 1 mg daily; adjusted according to response and side-effects; max. 2 mg/kg daily

Trihexyphenidyl (Non-proprietary) (PoM)

Tablets, trihexyphenidyl hydrochloride 2 mg, net price 84-tab pack = £6.31; 5 mg, 84-tab pack = £17.81, 100-tab pack = £17.15. Counselling, before or after food, driving, see notes above

Syrup, trihexyphenidyl hydrochloride 5 mg/5 mL, net price 200 mL = £20.00. Counselling, driving, see notes above

Excipients may include propylene glycol (see Excipients, p. 2)

4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders

Haloperidol can improve motor tics and symptoms of Tourette syndrome and related choreas (see section 4.2.1). Other treatments for Tourette syndrome include **pimozide** (p. 176) [unlicensed indication] (**important:** ECG monitoring required) and **sulpiride** (p. 176) [unlicensed indication].

Propranolol or another beta-adrenoceptor blocking drug (section 2.4) may be useful in treating essential tremor or tremor associated with anxiety or thyrotoxicosis.

Botulinum toxin type A should be used under specialist supervision. Treatment with botulinum toxin type A can be considered in children with an acquired non-progressive brain injury if rapid-onset spasticity causes postural or functional difficulties, and in children with spasticity in whom focal dystonia causes postural or functional difficulties or pain.

BOTULINUM TOXIN TYPE A

Cautions history of dysphagia or aspiration; chronic respiratory disorder; neuromuscular or neurological disorders (can lead to increased sensitivity and exaggerated muscle weakness including dysphagia and respiratory compromise); excessive weakness, inflammation or atrophy in target muscle; off-label use (fatal adverse events reported)

Contra-indications generalised disorders of muscle activity (e.g. myasthenia gravis); infection at injection site

Pregnancy avoid unless essential—toxicity in *animal* studies; avoid in women of child-bearing age unless using effective contraception

Breast-feeding low risk of systemic absorption but avoid unless essential

Side-effects increased electrophysiologic jitter in some distant muscles; misplaced injections may paralyse nearby muscle groups and excessive doses may paralyse distant muscles; influenza-like symptoms, *rarely* arrhythmias, myocardial infarction, seizures, hypersensitivity reactions including rash, pruritus and anaphylaxis, antibody formation (substantial deterioration in response); *very rarely* exaggerated muscle weakness, dysphagia, dysphonia, respiratory disorders, aspiration (see Counselling below)

Specific side-effects in paediatric cerebral palsy

Drowsiness, paraesthesia, urinary incontinence, myalgia

Indications and dose

In children over 2 years for dynamic equinus foot deformity caused by spasticity in ambulant paediatric cerebral palsy for dose consult product literature (**important:** information specific to **each individual preparation and not interchangeable**)

Counselling Children and carers should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties; they should be advised to seek immediate medical attention if swallowing, speech or breathing difficulties occur

Botox® (Allergan) [PmM]

Injection, powder for reconstitution, botulinum toxin type A complex, net price 50-unit vial = £77.50; 100-unit vial = £138.20; 200-unit vial = £276.40. Counselling, side-effects, see under Dose above

Dysport® (Ipsen) [PmM]

Injection, powder for reconstitution, botulinum type A toxin-haemagglutinin complex, net price 300-unit vial = £92.40; 500-unit vial = £154.00. Counselling, side-effects, see under Dose above

Guidelines on Clinical Management (2007) is available at www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf.

Neonatal abstinence syndrome Neonatal abstinence syndrome occurs at birth as a result of intra-uterine exposure to opioids or high-dose benzodiazepines.

Treatment is usually initiated if:

- feeding becomes a problem and tube feeding is required;
- there is profuse vomiting or watery diarrhoea;
- the baby remains very unsettled after two consecutive feeds despite gentle swaddling and the use of a pacifier.

Treatment involves weaning the baby from the drug on which it is dependent. **Morphine** or **methadone** (section 4.7.2) can be used in babies of mothers who have been taking opioids. Morphine is widely used because the dose can be easily adjusted, but methadone may provide smoother control of symptoms. Weaning babies from opioids usually takes 7–10 days.

Weaning babies from benzodiazepines that have a long half-life is difficult to manage; **chlorpromazine** (section 4.2.1) may be used in these situations but excessive sedation may occur. For babies who are dependent on barbiturates, phenobarbital (section 4.8.1) may be tried, although it does not control gastro-intestinal symptoms.

4.10.1 Alcohol dependence

Classification not used in *BNF for Children*.

4.10.2 Nicotine dependence

Smoking cessation interventions are a cost-effective way of reducing ill health and prolonging life. Smokers should be advised to stop and offered help with follow-up when appropriate. If possible, smokers should have access to smoking cessation services for behavioural support.

Therapy to aid smoking cessation is chosen according to the smoker's likely adherence, availability of counselling and support, previous experience of smoking-cessation aids, contra-indications and adverse effects of the preparations, and the smoker's preferences. Nicotine replacement therapy is an effective aid to smoking cessation. The use of nicotine replacement therapy in an individual who is already accustomed to nicotine introduces few new risks and it is widely accepted that there are no circumstances in which it is safer to smoke than to use nicotine replacement therapy.

Some individuals benefit from having more than one type of nicotine replacement therapy prescribed, such as a combination of transdermal and oral preparations.

Concomitant medication Cigarette smoking increases the metabolism of some medicines by stimulating the hepatic enzyme CYP1A2. When smoking is discontinued, the dose of these drugs, in particular theophylline p. 140 and some antipsychotics (including clozapine p. 178, olanzapine p. 179, chlorpromazine p. 174, and haloperidol p. 174), may need to be reduced. Regular monitoring for adverse effects is advised.

4.10 Drugs used in substance dependence

4.10.1 Alcohol dependence

4.10.2 Nicotine dependence

4.10.3 Opioid dependence

This section includes drugs used in the treatment of neonatal abstinence syndrome and cigarette smoking.

Treatment of alcohol or opioid dependence in children requires specialist management. The UK health departments have produced guidance on the treatment of drug misuse in the UK. *Drug Misuse and Dependence: UK*

Nicotine replacement therapy

Nicotine replacement therapy can be used in place of cigarettes after abrupt cessation of smoking, or alternatively to reduce the amount of cigarettes used in advance of making a quit attempt. Nicotine replacement therapy can also be used to minimise passive smoking, and to treat cravings and reduce compensatory smoking after enforced abstinence in smoke-free environments. Smokers who find it difficult to achieve abstinence should consult a healthcare professional for advice.

Choice Nicotine patches are a prolonged-release formulation and are applied for 16 hours (with the patch removed overnight) or for 24 hours. If the individual experiences strong cravings for cigarettes on waking, a 24-hour patch may be more suitable. Immediate-release nicotine preparations (gum, lozenges, sublingual tablets, inhalator, nasal spray, and oral spray) are used whenever the urge to smoke occurs or to prevent cravings.

The choice of nicotine replacement preparation depends largely on patient preference, and should take into account what preparations, if any, have been tried before. Patients with a high level of nicotine dependence, or who have failed with nicotine replacement therapy previously, may benefit from using a combination of an immediate-release preparation and patches to achieve abstinence.

All preparations are licensed for children over 12 years (with the exception of *Nicotinell*[®] lozenges which are licensed for children under 18 years only when recommended by a doctor).

Cautions Most warnings for nicotine replacement therapy also apply to continued cigarette smoking, but the risk of continued smoking outweighs any risks of using nicotine preparations. Nicotine replacement therapy should be used with caution in haemodynamically unstable patients hospitalised with severe arrhythmias, myocardial infarction, or cerebrovascular accident, and in patients with pheochromocytoma or uncontrolled hyperthyroidism. Care is also needed in individuals with diabetes mellitus—blood-glucose concentration should be monitored closely when initiating treatment.

Specific cautions for individual preparations are usually related to the local effect of nicotine. *Oral preparations* should be used with caution in patients with oesophagitis, gastritis, or peptic ulcers because swallowed nicotine can aggravate these conditions. The *gum* may also stick to and damage dentures. Acidic beverages, such as coffee or fruit juice, may decrease the absorption of nicotine through the buccal mucosa and should be avoided for 15 minutes before the use of oral nicotine replacement therapy. Care should be taken with the *inhalation cartridges* in patients with obstructive lung disease, chronic throat disease, or bronchospastic disease. The *nasal spray* can cause worsening of bronchial asthma. *Patches* should not be placed on broken skin and should be used with caution in patients with skin disorders.

Hepatic impairment Nicotine replacement therapy should be used with caution in moderate to severe hepatic impairment.

Renal impairment Nicotine replacement therapy should be used with caution in severe renal impairment.

Pregnancy The use of nicotine replacement therapy in pregnancy is preferable to the continuation of

smoking, but should be used only if smoking cessation without nicotine replacement fails. Intermittent therapy is preferable to patches but avoid liquorice-flavoured nicotine products. Patches are useful however, if the young woman is experiencing pregnancy-related nausea and vomiting. If patches are used, they should be removed before bed.

Breast-feeding Nicotine is present in milk; however, the amount to which the infant is exposed is small and less hazardous than second-hand smoke. Intermittent therapy is preferred.

Side-effects Some systemic effects occur on initiation of therapy, particularly if the individual is using high-strength preparations; however, the individual may confuse side-effects of the nicotine-replacement preparation with nicotine withdrawal symptoms. Common symptoms of nicotine withdrawal include malaise, headache, dizziness, sleep disturbance, coughing, influenza-like symptoms, depression, irritability, increased appetite, weight gain, restlessness, anxiety, drowsiness, aphthous ulcers, decreased heart rate, and impaired concentration.

Mild local reactions at the beginning of treatment are common because of the irritant effect of nicotine. *Oral preparations* and *inhalation cartridges* can cause irritation of the throat, *gum*, *lozenges*, and *oral spray* can cause increased salivation, and *patches* can cause minor skin irritation. The *nasal spray* commonly causes coughing, nasal irritation, epistaxis, sneezing, and watery eyes; the *oral spray* can cause watery eyes and blurred vision.

Gastro-intestinal disturbances are common and may be caused by swallowed nicotine. Nausea, vomiting, dyspepsia, and hiccup occur most frequently. Ulcerative stomatitis has also been reported. Dry mouth is a common side-effect of *lozenges*, *patches*, *oral spray*, and *sublingual tablets*. *Lozenges* cause diarrhoea, constipation, dysphagia, oesophagitis, gastritis, mouth ulcers, bloating, flatulence, and less commonly, taste disturbance, thirst, gingival bleeding, and halitosis. The *oral spray* may also cause abdominal pain, flatulence, and taste disturbance.

Palpitations may occur with nicotine replacement therapy and rarely *patches* and *oral spray* can cause arrhythmia. The *inhalator* can very rarely cause reversible atrial fibrillation. *Patches*, *lozenges*, and *oral spray* can cause chest pain.

Paraesthesia is a common side-effect of *oral spray*. Abnormal dreams can occur with *patches*; removal of the patch before bed may help. *Lozenges* and *oral spray* may cause rash and hot flushes. Sweating and myalgia can occur with *patches* and *oral spray*; the *patches* can also cause arthralgia.

Nicotine medicated chewing gum Individuals who smoke fewer than 20 cigarettes each day should use 1 piece of 2-mg strength gum when the urge to smoke occurs or to prevent cravings; individuals who smoke more than 20 cigarettes each day or who require more than 15 pieces of 2-mg strength gum each day should use the 4-mg strength. Individuals should not exceed 15 pieces of 4-mg strength gum daily. If attempting smoking cessation, treatment should continue for 3 months before reducing the dose.

Administration Chew the gum until the taste becomes strong, then rest it between the cheek and gum; when the taste starts to fade, repeat this process. One piece of gum lasts for approximately 30 minutes.

Nicotine inhalation cartridge The cartridges can be used when the urge to smoke occurs or to prevent cravings, up to a maximum of 12 cartridges of the 10-mg strength daily, or 6 cartridges of the 15-mg strength daily.

Administration Insert the cartridge into the device and draw in air through the mouthpiece; each session can last for approximately 5 minutes. The amount of nicotine from 1 puff of the cartridge is less than that from a cigarette, therefore it is necessary to inhale more often than when smoking a cigarette. A single 10-mg cartridge lasts for approximately 20 minutes of intense use; a single 15-mg cartridge lasts for approximately 40 minutes of intense use.

Nicotine lozenge One lozenge should be used every 1–2 hours when the urge to smoke occurs. Individuals who smoke less than 20 cigarettes each day should usually use the lower-strength lozenges; individuals who smoke more than 20 cigarettes each day and those who fail to stop smoking with the low-strength lozenges should use the higher-strength lozenges. Individuals should not exceed 15 lozenges daily. If attempting smoking cessation, treatment should continue for 6–12 weeks before attempting a reduction in dose.

Administration Slowly allow each lozenge to dissolve in the mouth; periodically move the lozenge from one side of the mouth to the other. Lozenges last for 10–30 minutes, depending on their size.

Nicotine sublingual tablets Individuals who smoke fewer than 20 cigarettes each day should initially use 1 tablet each hour, increased to 2 tablets each hour if necessary; individuals who smoke more than 20 cigarettes each day should use 2 tablets each hour. Individuals should not exceed 40 tablets daily. If attempting smoking cessation, treatment should continue for up to 3 months before reducing the dose.

Administration Each tablet should be placed under the tongue and allowed to dissolve.

Nicotine oral spray Individuals can use 1–2 sprays in the mouth when the urge to smoke occurs or to prevent cravings. Individuals should not exceed 2 sprays per episode (up to 4 sprays every hour), and a maximum of 64 sprays daily.

Administration The oral spray should be released into the mouth, holding the spray as close to the mouth as possible and avoiding the lips. The individual should not inhale while spraying and avoid swallowing for a few seconds after use.

Note If using the oral spray for the first time, or if unit not used for 2 or more days, prime the unit before administration.

Nicotine nasal spray Individuals can use 1 spray in each nostril when the urge to smoke occurs, up to twice every hour for 16 hours daily (maximum 64 sprays daily). If attempting smoking cessation, treatment should continue for 8 weeks before reducing the dose.

Administration Initially 1 spray should be used in both nostrils but when withdrawing from therapy, the dose can be gradually reduced to 1 spray in 1 nostril.

Nicotine transdermal patches As a general guide for smoking cessation, individuals who smoke more than 10 cigarettes daily should apply a high-strength patch daily for 6–8 weeks, followed by the medium strength patch for 2 weeks, and then the low-strength patch for the final 2 weeks; individuals who smoke fewer than 10 cigarettes daily can usually start with the

medium-strength patch for 6–8 weeks, followed by the low-strength patch for 2–4 weeks. A slower titration schedule can be used in patients who are not ready to quit but want to reduce cigarette consumption before a quit attempt.

If abstinence is not achieved, or if withdrawal symptoms are experienced, the strength of the patch used should be maintained or increased until the patient is stabilised. Individuals using the high-strength patch who experience excessive side-effects, that do not resolve within a few days, should change to a medium-strength patch for the remainder of the initial period and then use the low strength patch for 2–4 weeks.

Administration Patches should be applied on waking to dry, non-hairy skin on the hip, trunk, or upper arm and held in position for 10–20 seconds to ensure adhesion; place next patch on a different area and avoid using the same site for several days.

NICOTINE

Cautions see notes above; **interactions:** Appendix 1 (nicotine)

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

See notes above

Nicorette® (McNeil)

Tablets (sublingual) (*Nicorette Microtab®*), nicotine (as a cyclodextrin complex) 2 mg, net price starter pack of 2 × 15-tablet discs with dispenser = £4.83; pack of 100 = £13.12. Label: 26, counselling, administration, see notes above

Note Also available as *NicAssist®*

Chewing gum, sugar-free, nicotine (as resin) 2 mg, net price pack of 30 = £3.25, pack of 105 = £9.27, pack of 210 = £14.82; 4 mg, pack of 30 = £3.99, pack of 105 = £11.28, pack of 210 = £18.24. Counselling, administration, see notes above

Note Available in mint, freshfruit, freshmint, and icy white flavours (icy white flavour not available for pack size of 210 pieces). Also available as *NicAssist®*

Mint lozenge, sugar-free, nicotine (as bitartrate) 2 mg, net price pack of 24 = £2.55, pack of 96 = £8.29. Counselling, administration, see notes above

Patches, self-adhesive, beige, nicotine, '5 mg' patch (releasing approx. 5 mg/16 hours), net price 7 = £9.97; '10 mg' patch (releasing approx. 10 mg/16 hours), 7 = £9.97; '15 mg' patch (releasing approx. 15 mg/16 hours), 2 = £2.85, 7 = £9.97. Counselling, administration, see notes above

Note Also available as *NicAssist®*

Invisi patches, self-adhesive, beige, nicotine, '10 mg' patch (releasing approx. 10 mg/16 hours), net price 7 = £9.97; '15 mg' patch (releasing approx. 15 mg/16 hours), 7 = £9.97; '25 mg' patch (releasing approx. 25 mg/16 hours), 7 = £9.97. Counselling, administration, see notes above

Note Also available as *NicAssist® Translucent patches*

Oral spray (*Nicorette Quickmist® mouthspray*), nicotine 1 mg/metered dose, net price 150-dose pack = £12.12, 2 × 150-dose pack = £19.14. Counselling, administration, see notes above

Note Contains < 100 mg ethanol per dose

Nasal spray, nicotine 500 micrograms/metered spray, net price 200-spray unit = £13.40. Counselling, administration, see notes above

Note Also available as *NicAssist*®

Inhalator (nicotine-impregnated plug for use in inhalator mouthpiece), nicotine 10 mg/cartridge, net price 6-cartridge pack = £4.46, 42-cartridge pack = £14.65; 15 mg/cartridge, 4-cartridge pack = £4.14, 20-cartridge pack = £14.67, 36-cartridge pack = £22.33. Counselling, administration, see notes above

Note Also available as *NicAssist*®

Nicotinell® (Novartis Consumer Health)

Chewing gum, sugar-free, nicotine (as polacrillin complex) 2 mg, net price pack of 12 = £1.71, pack of 24 = £3.01, pack of 72 = £6.69, pack of 96 = £8.26, pack of 204 = £14.23; 4 mg, pack of 12 = £1.70, pack of 24 = £3.30, pack of 72 = £8.29, pack of 96 = £10.26. Counselling, administration, see notes above

Note Also available in fruit, liquorice, icemint, and mint flavours

Mint lozenge, sugar-free, nicotine (as bitartrate) 1 mg, net price pack of 12 = £1.59, pack of 36 = £4.27, pack of 96 = £9.12; 2 mg, pack of 12 = £1.99, pack of 36 = £4.95, pack of 96 = £10.60. Counselling, administration, see notes above

Excipients include aspartame (section 9.4.1)

TTS Patches, self-adhesive, all yellowish-ochre, nicotine, '10' patch (releasing approx. 7 mg/24 hours), net price 7 = £9.12; '20' patch (releasing approx. 14 mg/24 hours), 2 = £2.57, 7 = £9.40; '30' patch (releasing approx. 21 mg/24 hours), 2 = £2.85, 7 = £9.97, 21 = £24.51. Counselling, administration, see notes above

NiQuitin® (GSK Consumer Healthcare)

Chewing gum, sugar-free, mint-flavour, nicotine 2 mg (white), net price pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55; 4 mg (yellow), pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55. Counselling, administration, see notes above

Lozenges, sugar-free, nicotine (as resinate) 1.5 mg (cherry- and mint-flavoured), net price pack of 20 = £3.18, pack of 60 = £8.93; 2 mg (mint-flavoured), pack of 36 = £5.12, pack of 72 = £9.97; 4 mg (mint-flavoured), pack of 20 = £3.18, pack of 36 = £5.12, pack of 60 = £8.93, pack of 72 = £9.97. Counselling, administration, see notes above

Excipients include aspartame (section 9.4.1); contains 0.65 mmol Na⁺/lozenge

Note Nicotine (as resinate) also available as *Niquitin*® Prequit lozenges and *Niquitin*® Minis lozenges

Patches, self-adhesive, pink/beige, nicotine '7 mg' patch (releasing approx. 7 mg/24 hours), net price 7 = £9.97; '14 mg' patch (releasing approx. 14 mg/24 hours), 7 = £9.97; '21 mg' patch (releasing approx. 21 mg/24 hours), 7 = £9.97, 14 = £18.79. Counselling, administration, see notes above

Note Also available as a clear patch

4.10.3 Opioid dependence

Classification not used in *BNF for Children*.

4.11 Drugs for dementia

Classification not used in *BNF for Children*.

5 Infections

5.1 Antibacterial drugs	247
5.1.1 Penicillins	261
5.1.1.1 Benzylpenicillin and phenoxymethylpenicillin	261
5.1.1.2 Penicillinase-resistant penicillins	263
5.1.1.3 Broad-spectrum penicillins	264
5.1.1.4 Antipseudomonal penicillins	268
5.1.1.5 Mecillinams	269
5.1.2 Cephalosporins, carbapenems, and other beta-lactams	269
5.1.2.1 Cephalosporins	269
5.1.2.2 Carbapenems	275
5.1.2.3 Other beta-lactam antibiotics	277
5.1.3 Tetracyclines	277
5.1.4 Aminoglycosides	280
5.1.5 Macrolides	283
5.1.6 Clindamycin	287
5.1.7 Some other antibacterials	287
5.1.8 Sulfonamides and trimethoprim	292
5.1.9 Antituberculosis drugs	294
5.1.10 Antileprotic drugs	299
5.1.11 Metronidazole	299
5.1.12 Quinolones	301
5.1.13 Urinary-tract infections	303
5.2 Antifungal drugs	304
5.2.1 Triazole antifungals	305
5.2.2 Imidazole antifungals	309
5.2.3 Polyene antifungals	309
5.2.4 Echinocandin antifungals	310
5.2.5 Other antifungals	311
5.3 Antiviral drugs	313
5.3.1 HIV infection	313
5.3.2 Herpesvirus infections	325
5.3.2.1 Herpes simplex and varicella-zoster infection	325
5.3.2.2 Cytomegalovirus infection	328
5.3.3 Viral hepatitis	329
5.3.4 Influenza	330
5.3.5 Respiratory syncytial virus	332
5.4 Antiprotozoal drugs	334
5.4.1 Antimalarials	334
5.4.2 Amoebicides	347
5.4.3 Trichomonads	348
5.4.4 Antigiardial drugs	348

5.4.5 Leishmaniases	348
5.4.6 Trypanocides	349
5.4.7 Drugs for toxoplasmosis	349
5.4.8 Drugs for pneumocystis pneumonia	350
5.5 Anthelmintics	352
5.5.1 Drugs for threadworms	352
5.5.2 Ascaricides	353
5.5.3 Drugs for tapeworm infections	353
5.5.4 Drugs for hookworms	353
5.5.5 Schistosomides	353
5.5.6 Filaricides	354
5.5.7 Drugs for cutaneous larva migrans	354
5.5.8 Drugs for strongyloidiasis	354

This chapter includes advice on the drug management of the following:

anthrax, p. 301
bacterial infections: table 1, summary of antibacterial treatment, p. 248
bacterial infections: table 2, summary of antibacterial prophylaxis, p. 258
Lyme disease, p. 264
MRSA infections, p. 263
oral infections, p. 247 and p. 255

Notifiable diseases

Doctors must notify the Proper Officer of the local authority (usually the consultant in communicable disease control) when attending a patient suspected of suffering from any of the diseases listed below; a form is available from the Proper Officer.

Anthrax	Mumps
Botulism	Paratyphoid fever
Brucellosis	Plague
Cholera	Poliomyelitis, acute
Diarrhoea (infectious bloody)	Rabies
Diphtheria	Rubella
Encephalitis, acute	SARS
Food poisoning	Scarlet fever
Haemolytic uraemic syndrome	Smallpox
Haemorrhagic fever (viral)	Streptococcal disease (Group A, invasive)
Hepatitis, viral	Tetanus
Legionnaires' disease	Tuberculosis
Leprosy	Typhoid fever
Malaria	Typhus
Measles	Whooping cough
Meningitis	Yellow fever
Meningococcal septicaemia	

Note

It is good practice for doctors to also inform the consultant in communicable disease control of instances of

other infections (e.g. psittacosis) where there could be a public health risk.

5.1 Antibacterial drugs

5.1.1 Penicillins

5.1.2 Cephalosporins, carbapenems, and other beta-lactams

5.1.3 Tetracyclines

5.1.4 Aminoglycosides

5.1.5 Macrolides

5.1.6 Clindamycin

5.1.7 Some other antibacterials

5.1.8 Sulfonamides and trimethoprim

5.1.9 Antituberculosis drugs

5.1.10 Antileprotic drugs

5.1.11 Metronidazole

5.1.12 Quinolones

5.1.13 Urinary-tract infections

Choice of a suitable drug Before selecting an antibacterial the clinician must first consider two factors—the child and the known or likely causative organism. Factors related to the child which must be considered include history of allergy, renal and hepatic function, susceptibility to infection (i.e. whether immunocompromised), ability to tolerate drugs by mouth, severity of illness, ethnic origin, age and, if an adolescent female, whether pregnant, breast-feeding or taking an oral contraceptive.

The known or likely organism and its antibacterial sensitivity, in association with the above factors, will suggest one or more antibacterials, the final choice depending on the microbiological, pharmacological, and toxicological properties.

The principles involved in selection of an antibacterial must allow for a number of variables including age, changing renal and hepatic function, increasing bacterial resistance, and information on side-effects. Duration of therapy, dosage, and route of administration depend on site, type and severity of infection and response.

Antibacterial policies Local policies often limit the antibacterials that may be used to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the microbiologist or paediatric infectious diseases specialist.

Before starting therapy The following principles should be considered before starting:

- Viral infections should not be treated with antibacterials. However, antibacterials may be indicated for treatment of secondary bacterial infection (e.g. bacterial pneumonia secondary to influenza);
- Samples should be taken for culture and sensitivity testing whenever possible; 'blind' antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis;
- Knowledge of **prevalent organisms** and their current **sensitivity** is of great help in choosing an antibacterial before bacteriological confirmation is

available. Generally, narrow-spectrum antibacterials are preferred to broad-spectrum antibacterials unless there is a clear clinical indication (e.g. life-threatening sepsis);

- The **dose** of an antibacterial varies according to a number of factors including age, weight, hepatic function, renal function, and severity of infection. The prescribing of the so-called 'standard' dose in serious infections may result in failure of treatment or even death of the patient; therefore it is important to prescribe a dose appropriate to the condition. An inadequate dose may also increase the likelihood of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored;
- The **route** of administration of an antibacterial often depends on the severity of the infection. Life-threatening infections often require intravenous therapy. Antibacterials that are well absorbed may be given by mouth even for some serious infections. Parenteral administration is also appropriate when the oral route cannot be used (e.g. because of vomiting) or if absorption is inadequate (e.g. in neonates and young children). Whenever possible painful intramuscular injections should be avoided in children;
- **Duration** of therapy depends on the nature of the infection and the response to treatment. Courses should not be unduly prolonged because they encourage resistance, they may lead to side-effects and they are costly. However, in certain infections such as tuberculosis or osteomyelitis it may be necessary to treat for prolonged periods. The prescription for an antibacterial should specify the duration of treatment or the date when treatment is to be reviewed.

Oral bacterial infections Antibacterial drugs should only be prescribed for the *treatment* of oral infections on the basis of defined need. They may be used in conjunction with (but not as an alternative to) other appropriate measures, such as providing drainage or extracting a tooth.

The 'blind' prescribing of an antibacterial for unexplained pyrexia, cervical lymphadenopathy, or facial swelling can lead to difficulty in establishing the diagnosis. A sample should always be taken for bacteriology in the case of severe oral infection.

Oral infections which may require antibacterial treatment include acute periapical or periodontal abscess, cellulitis, acutely created oral-antral communication (and acute sinusitis), severe pericoronitis, localised osteitis, acute necrotising ulcerative gingivitis, and destructive forms of chronic periodontal disease. Most of these infections are readily resolved by the early establishment of drainage and removal of the cause (typically an infected necrotic pulp). Antibacterials may be required if treatment has to be delayed, in immunocompromised patients, or in those with conditions such as diabetes; see also Table 1, section 5.1. Certain rarer infections including bacterial sialadenitis, osteomyelitis, actinomycosis, and infections involving fascial spaces such as Ludwig's angina, require antibiotics and specialist hospital care.

Antibacterial drugs may also be useful after dental surgery in some cases of spreading infection. Infection may spread to involve local lymph nodes, to fascial spaces (where it can cause airway obstruction), or into the bloodstream (where it can lead to cavernous sinus thrombosis and other serious complications). Extension of an infection can also lead to maxillary sinusitis; osteomyelitis is a complication, which usually arises when host resistance is reduced.

If the oral infection fails to respond to antibacterial treatment within 48 hours the antibacterial should be changed, preferably on the basis of bacteriological investigation. Failure to respond may also suggest an incorrect diagnosis, lack of essential additional measures (such as drainage), poor host resistance, or poor patient compliance.

Combination of a penicillin (or a macrolide) with metronidazole may sometimes be helpful for the treatment of severe or resistant oral infections.

See also **Penicillins** (section 5.1.1), **Cephalosporins** (section 5.1.2.1), **Tetracyclines** (section 5.1.3), **Macrolides** (section 5.1.5), **Clindamycin** (section 5.1.6), **Metronidazole** (section 5.1.11), **Fusidic acid** (section 13.10.1.2).

Superinfection In general, broad-spectrum antibacterial drugs such as the cephalosporins are more likely to be associated with adverse reactions related to

the selection of resistant organisms e.g. *fungus infections* or *antibiotic-associated colitis* (pseudomembranous colitis); other problems associated with superinfection include vaginitis and pruritus ani.

Therapy Suggested treatment is shown in Table 1. When the pathogen has been isolated treatment may be changed to a more appropriate antibacterial if necessary. If no bacterium is cultured the antibacterial can be continued or stopped on clinical grounds. Infections for which prophylaxis is useful are listed in table 2.

Switching from parenteral to oral treatment

The ongoing parenteral administration of an antibacterial should be reviewed regularly. In older children it may be possible to switch to an oral antibacterial; in neonates and infants this should be done more cautiously because of the relatively high incidence of bacteraemia and the possibility of variable oral absorption.

Prophylaxis Infections for which antibacterial prophylaxis is useful are listed in Table 2. In most situations, only a short course of prophylactic antibacterial is needed. Longer-term antibacterial prophylaxis is appropriate in specific indications such as vesico-ureteric reflux

Table 1. Summary of antibacterial therapy

If treating a patient suspected of suffering from a notifiable disease, the consultant in communicable disease control should be informed (see p. 246)

Gastro-intestinal system

Gastro-enteritis

Frequently self-limiting and may not be bacterial.

Antibacterial not usually indicated

Campylobacter enteritis

Frequently self-limiting; treat if immunocompromised or if severe infection.

Clarithromycin¹

Alternative, ciprofloxacin

Strains with decreased sensitivity to ciprofloxacin isolated frequently

Salmonella (non-typhoid)

Treat invasive or severe infection. Do not treat less severe infection unless there is a risk of developing invasive infection (e.g. immunocompromised children, those with haemoglobinopathy, or children under 6 months of age).

Ciprofloxacin or cefotaxime

Shigellosis

Antibacterial not indicated for mild cases.

Azithromycin or ciprofloxacin

Alternatives if micro-organism sensitive, amoxicillin or trimethoprim

1. Where clarithromycin is suggested azithromycin or erythromycin may be used

Typhoid fever

Infections from Middle-East, South Asia, and South-East Asia may be multiple-antibacterial-resistant and sensitivity should be tested.

Cefotaxime¹

Azithromycin may be an alternative in mild or moderate disease caused by multiple-antibacterial-resistant micro-organisms

Alternative if micro-organism sensitive, ciprofloxacin or chloramphenicol

Clostridium difficile infection

For first episode of mild to moderate infection, oral metronidazole

Suggested duration of treatment 10–14 days

For second or subsequent episode of infection, for severe infection, for infection not responding to metronidazole, or in children intolerant of metronidazole, oral vancomycin

Suggested duration of treatment 10–14 days

For infection not responding to vancomycin, or for life-threatening infection, or in patients with ileus, oral vancomycin + i/v metronidazole

Suggested duration of treatment 10–14 days

Necrotising enterocolitis in neonates

Benzylpenicillin + gentamicin + metronidazole *or* amoxicillin² + gentamicin + metronidazole *or* amoxicillin² + cefotaxime + metronidazole

Peritonitis

A cephalosporin + metronidazole *or* amoxicillin + gentamicin + metronidazole *or* piperacillin with tazobactam alone

Peritonitis: peritoneal dialysis-associated

Vancomycin³ + ceftazidime added to dialysis fluid *or* vancomycin added to dialysis fluid + ciprofloxacin by mouth

Suggested duration of treatment 14 days or longer

Cardiovascular system**Endocarditis: initial 'blind' therapy**

Flucloxacillin (*or* benzylpenicillin if symptoms less severe) + gentamicin

If cardiac prostheses present, or if penicillin-allergic, or if methicillin-resistant Staphylococcus aureus suspected, vancomycin + rifampicin + gentamicin

Endocarditis caused by staphylococci

Flucloxacillin

Add rifampicin for at least 2 weeks in prosthetic valve endocarditis.

Suggested duration of treatment at least 4 weeks (at least 6 weeks for prosthetic valve endocarditis)

If penicillin-allergic or if methicillin-resistant Staphylococcus aureus, vancomycin + rifampicin

Suggested duration of treatment at least 4 weeks (at least 6 weeks for prosthetic valve endocarditis)

Native-valve endocarditis caused by fully-sensitive streptococci (e.g. viridans streptococci)

Benzylpenicillin

Suggested duration of treatment 4 weeks

Alternative if a large vegetation, intracardial abscess, or infected emboli are absent, benzylpenicillin + gentamicin

Suggested duration of treatment 2 weeks

If penicillin-allergic, vancomycin

Suggested duration of treatment 4 weeks

1. Where cefotaxime is suggested ceftriaxone may be used

2. Where amoxicillin is suggested ampicillin may be used

3. Where vancomycin is suggested teicoplanin may be used

Native-valve endocarditis caused by less-sensitive streptococci

Benzylpenicillin + gentamicin

Suggested duration of treatment 4–6 weeks (stop gentamicin after 2 weeks for micro-organisms moderately sensitive to penicillin)*If aminoglycoside cannot be used and if streptococci moderately sensitive to penicillin, benzylpenicillin**Suggested duration of treatment* 4 weeks*If penicillin-allergic or highly penicillin-resistant, vancomycin¹ + gentamicin**Suggested duration of treatment* 4–6 weeks (stop gentamicin after 2 weeks for micro-organisms moderately sensitive to penicillin)**Prosthetic valve endocarditis caused by streptococci**

Benzylpenicillin + gentamicin

Suggested duration of treatment at least 6 weeks (stop gentamicin after 2 weeks if micro-organisms fully sensitive to penicillin)*If penicillin-allergic or highly penicillin-resistant, vancomycin¹ + gentamicin**Suggested duration of treatment* at least 6 weeks (stop gentamicin after 2 weeks if micro-organisms fully sensitive to penicillin)**Endocarditis caused by enterococci (e.g. *Enterococcus faecalis*)**Amoxicillin² + gentamicin*If gentamicin-resistant, substitute gentamicin with streptomycin.**Suggested duration of treatment* at least 4 weeks (at least 6 weeks for prosthetic valve endocarditis)*If penicillin-allergic or penicillin-resistant, vancomycin¹ + gentamicin**If gentamicin-resistant, substitute gentamicin with streptomycin.**Suggested duration of treatment* at least 4 weeks (at least 6 weeks for prosthetic valve endocarditis)**Endocarditis caused by haemophilus, actinobacillus, cardiobacterium, eikenella, and kingella species ('HACEK' micro-organisms)**Amoxicillin² + gentamicin*Suggested duration of treatment* 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks*If amoxicillin-resistant, ceftriaxone + gentamicin**Suggested duration of treatment* 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks**Respiratory system*****Haemophilus influenzae* epiglottitis**Cefotaxime³*If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol***Pneumonia: community-acquired**

Children under 2 years with mild symptoms of lower respiratory tract infection (particularly those vaccinated with pneumococcal polysaccharide conjugate vaccine and haemophilus type b conjugate vaccine) are unlikely to have pneumonia; antibacterial treatment may be considered if symptoms persist

*Neonate, benzylpenicillin + gentamicin**Child 1 month–18 years, amoxicillin² by mouth**Pneumococci with decreased penicillin sensitivity have been isolated in the UK, but are not common.**If no response to treatment, add clarithromycin⁴**If staphylococci suspected (e.g. in influenza or measles), give by mouth amoxicillin + flucloxacillin or co-amoxiclav alone**If septicaemia, complicated pneumonia, or if oral administration not possible, initiate treatment with i/v amoxicillin or i/v co-amoxiclav or i/v cefuroxime or i/v cefotaxime³**Suggested duration of treatment* 7 days (may extend treatment to 14 days in some cases e.g. if staphylococci suspected)*Child 1 month–18 years, if penicillin-allergic, clarithromycin⁴**Suggested duration of treatment* 7 days (may extend treatment to 14 days in some cases e.g. if staphylococci suspected)

1. Where vancomycin is suggested teicoplanin may be used

2. Where amoxicillin is suggested ampicillin may be used

3. Where cefotaxime is suggested ceftriaxone may be used

4. Where clarithromycin is suggested azithromycin or erythromycin may be used

Pneumonia possibly caused by atypical pathogens**Clarithromycin¹***Suggested duration of treatment* 10–14 days*Alternative for chlamydial or mycoplasma infections in children over 12 years, doxycycline**Suggested duration of treatment* 10–14 days**Pneumonia: hospital-acquired**

Early-onset infection (less than 5 days after admission to hospital), treat as for severe community-acquired pneumonia of unknown aetiology; if life-threatening infection, or if recent history of antibacterial treatment, or if resistant organisms suspected, treat as for late-onset hospital-acquired pneumonia

Late-onset infection (more than 5 days after admission to hospital), an antipseudomonal penicillin (e.g. piperacillin with tazobactam) or another antipseudomonal beta-lactam

If methicillin-resistant *Staphylococcus aureus* suspected, add vancomycin.*If* severe illness caused by *Pseudomonas aeruginosa*, add an aminoglycoside.*Suggested duration of treatment* 7 days (longer if *Pseudomonas aeruginosa* confirmed)**Cystic fibrosis****Staphylococcal lung infection in cystic fibrosis****Flucloxacillin***If* child already taking flucloxacillin prophylaxis or if severe exacerbation, add sodium fusidate or rifampicin; use flucloxacillin at treatment dose*If* penicillin-allergic, clarithromycin¹ or clindamycin*Use* clarithromycin only if micro-organism sensitive**Haemophilus influenzae lung infection in cystic fibrosis****Amoxicillin or a broad-spectrum cephalosporin***In* severe exacerbation use a third-generation cephalosporin (e.g. cefotaxime)**Pseudomonal lung infection in cystic fibrosis****Ciprofloxacin + nebulised colistimethate sodium***For* severe exacerbation, an antipseudomonal beta-lactam antibacterial + parenteral tobramycin**Central nervous system****Meningitis: initial empirical therapy**

- Transfer patient to hospital urgently.
- If meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) suspected, benzylpenicillin (see p. 262 for dose) should be given before transfer to hospital, so long as this does not delay the transfer. If a patient with suspected bacterial meningitis without non-blanching rash cannot be transferred to hospital urgently, benzylpenicillin (see p. 262 for dose) should be given before the transfer. Cefotaxime (section 5.1.2) may be an alternative in penicillin allergy; chloramphenicol (section 5.1.7) may be used if history of immediate hypersensitivity reaction to penicillins or to cephalosporins.
- In hospital, consider adjunctive treatment with dexamethasone (section 6.3.2), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial; avoid dexamethasone in septic shock, meningococcal septicaemia, or if immunocompromised, or in meningitis following surgery.
- In hospital, if aetiology unknown

Neonate and child 1–3 months, cefotaxime² + amoxicillin³*Consider* adding vancomycin if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci*Suggested duration of treatment* at least 14 days**Child 3 months–18 years, cefotaxime²***Consider* adding vancomycin if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci*Suggested duration of treatment* at least 10 days

1. Where clarithromycin is suggested azithromycin or erythromycin may be used

2. Where cefotaxime is suggested ceftriaxone may be used

3. Where amoxicillin is suggested ampicillin may be used

Meningitis caused by group B streptococcusBenzylpenicillin + gentamicin or cefotaxime¹ alone*Suggested duration of treatment* at least 14 days; stop gentamicin after 5 days**Meningitis caused by meningococci**Benzylpenicillin or cefotaxime¹*Suggested duration of treatment* 7 days.

To eliminate nasopharyngeal carriage in patients treated with benzylpenicillin or cefotaxime see Table 2, section 5.1

*If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol**Suggested duration of treatment* 7 days.

To eliminate nasopharyngeal carriage see Table 2, section 5.1

Meningitis caused by pneumococciCefotaxime¹

Consider adjunctive treatment with dexamethasone (section 6.3.2), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial (may reduce penetration of vancomycin into cerebrospinal fluid).

If micro-organism penicillin-sensitive, replace cefotaxime with benzylpenicillin.

If micro-organism highly penicillin- and cephalosporin-resistant, add vancomycin and if necessary rifampicin.

Suggested duration of antibacterial treatment 14 days**Meningitis caused by *Haemophilus influenzae***Cefotaxime¹

Consider adjunctive treatment with dexamethasone (section 6.3.2), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.

Suggested duration of antibacterial treatment 10 days.For *H. influenzae* type b give rifampicin for 4 days before hospital discharge to those under 10 years of age or to those in contact with vulnerable household contacts (see Table 2, section 5.1)*If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, or if micro-organism resistant to cefotaxime, chloramphenicol*

Consider adjunctive treatment with dexamethasone (section 6.3.2), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.

Suggested duration of antibacterial treatment 10 days.For *H. influenzae* type b give rifampicin for 4 days before hospital discharge to those under 10 years of age or to those in contact with vulnerable household contacts (see Table 2, section 5.1)**Meningitis caused by *Listeria***Amoxicillin² + gentamicin*Suggested duration of treatment* 21 days.

Consider stopping gentamicin after 7 days

*If history of immediate hypersensitivity reaction to penicillin, co-trimoxazole**Suggested duration of treatment* 21 days**Urinary tract****Urinary-tract infection***Child under 3 months of age, i/v amoxicillin² + gentamicin or i/v cephalosporin alone**Child over 3 months of age with uncomplicated lower urinary-tract infection, trimethoprim or nitrofurantoin**Suggested duration of treatment* 3 days.

Re-assess child if unwell 24–48 hours after initial assessment

Child over 3 months of age, alternative for uncomplicated lower urinary-tract infection, amoxicillin² or oral cephalosporin (e.g. cefalexin)

Use amoxicillin only if micro-organism sensitive.

Suggested duration of treatment 3 days.

Re-assess child if unwell 24–48 hours after initial assessment

*Child over 3 months of age with acute pyelonephritis, a cephalosporin or co-amoxiclav**Suggested duration of treatment* 7–10 days

1. Where cefotaxime is suggested ceftriaxone may be used

2. Where amoxicillin is suggested ampicillin may be used

Genital system

Uncomplicated genital chlamydial infection, non-gonococcal urethritis, and non-specific genital infection

Contact tracing recommended.

Child under 12 years, erythromycin

Suggested duration of treatment 14 days

Child 12–18 years, azithromycin or doxycycline

Suggested duration of treatment azithromycin as a single dose or doxycycline for 7 days

Child 12–18 years, alternative, erythromycin

Suggested duration of treatment 14 days

Gonorrhoea: uncomplicated

Contact tracing recommended. Consider chlamydia co-infection. Choice of antibacterial depends on locality where infection acquired.

Child under 12 years, ceftriaxone

Suggested duration of treatment single-dose

Child 12–18 years, cefixime

Suggested duration of treatment single-dose

Child 12–18 years, alternative if micro-organism sensitive, ciprofloxacin

Suggested duration of treatment single-dose

Child 12–18 years with pharyngeal infection, ceftriaxone

Suggested duration of treatment single-dose

Pelvic inflammatory disease

Contact tracing recommended

Child 2–12 years, erythromycin + metronidazole + i/m ceftriaxone

Suggested duration of treatment 14 days (use i/m ceftriaxone as a single dose)

Child 12–18 years, doxycycline + metronidazole + i/m ceftriaxone

If severely ill, seek specialist advice.

Suggested duration of treatment 14 days (use i/m ceftriaxone as a single dose)

Neonatal congenital syphilis

Benzylpenicillin

Also consider treating neonates with suspected congenital syphilis whose mothers were treated inadequately for syphilis, or whose mothers were treated for syphilis in the 4 weeks before delivery, or whose mothers were treated with non-penicillin antibacterials for syphilis.

Suggested duration of treatment 10 days

Syphilis

Contact tracing recommended.

Child under 12 years, benzylpenicillin or procaine benzylpenicillin [unlicensed]

Suggested duration of treatment 10 days

Child 12–18 years, early syphilis (infection of less than 2 years), benzathine benzylpenicillin [unlicensed]

Suggested duration of treatment single-dose (repeat dose after 7 days for females in the third trimester of pregnancy)

Child 12–18 years, alternatives for early syphilis, doxycycline or erythromycin

Suggested duration of treatment 14 days

Child 12–18 years, late latent syphilis (asymptomatic infection of more than 2 years), benzathine benzylpenicillin [unlicensed]

Suggested duration of treatment once weekly for 2 weeks

Child 12–18 years, alternative for late latent syphilis, doxycycline

Suggested duration of treatment 28 days

Child 12–18 years who is an asymptomatic contact of a patient with infectious syphilis, doxycycline

Suggested duration of treatment 14 days

Blood**Septicaemia**

Neonate less than 72 hours old, benzylpenicillin + gentamicin

If Gram-negative septicaemia suspected, use benzylpenicillin + gentamicin + cefotaxime; stop benzylpenicillin if Gram-negative infection confirmed.

Suggested duration of treatment usually 7 days

Neonate more than 72 hours old, flucloxacillin + gentamicin or amoxicillin¹ + cefotaxime

Suggested duration of treatment usually 7 days

Child 1 month–18 years with community-acquired septicaemia, aminoglycoside + amoxicillin¹ or cefotaxime² alone

If pseudomonas or resistant micro-organisms suspected, use a broad-spectrum antipseudomonal beta-lactam antibacterial.

If anaerobic infection suspected, add metronidazole.

If Gram-positive infection suspected, add flucloxacillin or vancomycin³.

Suggested duration of treatment at least 5 days

Child 1 month–18 years with hospital-acquired septicaemia, a broad-spectrum antipseudomonal beta-lactam antibacterial (e.g. piperacillin with tazobactam, ticarcillin with clavulanic acid, imipenem with cilastatin, or meropenem)

If pseudomonas suspected, or if multiple-resistant organisms suspected, or if severe sepsis, add aminoglycoside.

If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin³.

If anaerobic infection suspected, add metronidazole to a broad-spectrum cephalosporin.

Suggested duration of treatment at least 5 days

Septicaemia related to vascular catheter

Vancomycin³

If Gram-negative sepsis suspected, especially in the immunocompromised, add a broad-spectrum antipseudomonal beta-lactam.

Consider removing vascular catheter, particularly if infection caused by *Staphylococcus aureus*, pseudomonas, or candida

Meningococcal septicaemia

If meningococcal disease suspected, a single dose of benzylpenicillin (see p. 262 for dose) should be given before urgent transfer to hospital, so long as this does not delay the transfer; cefotaxime (section 5.1.2) may be an alternative in penicillin allergy; chloramphenicol may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins.

Benzylpenicillin or cefotaxime²

To eliminate nasopharyngeal carriage in patients treated with benzylpenicillin or cefotaxime see Table 2, section 5.1

If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol

To eliminate nasopharyngeal carriage see Table 2, section 5.1

Musculoskeletal system**Osteomyelitis**

Seek specialist advice if chronic infection or prostheses present.

Flucloxacillin

Consider adding fusidic acid or rifampicin for initial 2 weeks.

Suggested duration of treatment 6 weeks for acute infection

If penicillin-allergic, clindamycin

Consider adding fusidic acid or rifampicin for initial 2 weeks.

Suggested duration of treatment 6 weeks for acute infection

*If meticillin-resistant *Staphylococcus aureus* suspected, vancomycin³*

Consider adding fusidic acid or rifampicin for initial 2 weeks.

Suggested duration of treatment 6 weeks for acute infection

1. Where amoxicillin is suggested ampicillin may be used

2. Where cefotaxime is suggested ceftriaxone may be used

3. Where vancomycin is suggested teicoplanin may be used

Septic arthritis

Seek specialist advice if prostheses present.

Flucloxacillin

Suggested duration of treatment 4–6 weeks (longer if infection complicated)

If penicillin-allergic, clindamycin

Suggested duration of treatment 4–6 weeks (longer if infection complicated)

If meticillin-resistant *Staphylococcus aureus* suspected, vancomycin¹

Suggested duration of treatment 4–6 weeks (longer if infection complicated)

If gonococcal arthritis or Gram-negative infection suspected, cefotaxime²

Suggested duration of treatment 4–6 weeks (longer if infection complicated; treat gonococcal infection for 2 weeks)

Eye**Purulent conjunctivitis**

Chloramphenicol eye drops

See also section 11.3.1

Congenital chlamydial conjunctivitis

Erythromycin (by mouth)

Suggested duration of treatment 14 days

Congenital gonococcal conjunctivitis

Cefotaxime²

Suggested duration of treatment single-dose

Ear, nose, and oropharynx**Pericoronitis**

Antibacterial required only in presence of systemic features of infection, or of trismus, or persistent swelling despite local treatment.

Metronidazole

Suggested duration of treatment 3 days or until symptoms resolve

Alternative, amoxicillin

Suggested duration of treatment 3 days or until symptoms resolve

Gingivitis: acute necrotising ulcerative

Antibacterial required only if systemic features of infection.

Metronidazole

Suggested duration of treatment 3 days or until symptoms resolve

Alternative, amoxicillin

Suggested duration of treatment 3 days or until symptoms resolve

Periapical or periodontal abscess

Antibacterial required only in severe disease with cellulitis or if systemic features of infection.

Amoxicillin

Suggested duration of treatment 5 days

Alternative, metronidazole

Suggested duration of treatment 5 days

Periodontitis

Antibacterial used as an adjunct to debridement in severe disease or disease unresponsive to local treatment alone.

Metronidazole

Alternative in child over 12 years, doxycycline

1. Where vancomycin is suggested teicoplanin may be used

2. Where cefotaxime is suggested ceftriaxone may be used

Throat infections

Most throat infections are caused by viruses and many do not require antibacterial therapy. Consider antibacterial, if history of valvular heart disease, if marked systemic upset, if peritonsillar cellulitis or abscess, or if at increased risk from acute infection (e.g. in immunosuppression, cystic fibrosis); prescribe antibacterial for beta-haemolytic streptococcal pharyngitis.

Phenoxymethylpenicillin

In severe infection, initial parenteral therapy with benzylpenicillin, then oral therapy with phenoxymethylpenicillin or amoxicillin¹. **Avoid** amoxicillin if possibility of glandular fever, see section 5.1.1.3.

Suggested duration of treatment 10 days

If penicillin-allergic, clarithromycin²

Suggested duration of treatment 10 days

Sinusitis

Antibacterial should usually be used only for persistent symptoms and purulent discharge lasting at least 7 days or if severe symptoms. Also, consider antibacterial for those at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis).

Amoxicillin¹ or clarithromycin²

Suggested duration of treatment 7 days.

Consider oral co-amoxiclav if no improvement after 48 hours.

In severe infection, initial parenteral therapy with co-amoxiclav or cefuroxime may be required

Otitis externa

Consider systemic antibacterial if spreading cellulitis or child systemically unwell.

For topical preparations see section 12.1.1.

Flucloxacillin

If penicillin-allergic, clarithromycin²

If pseudomonas suspected, ciprofloxacin (or an aminoglycoside)

Otitis media

Many infections caused by viruses. Most uncomplicated cases resolve without antibacterial treatment. In children without systemic features, antibacterial treatment may be started after 72 hours if no improvement. Consider earlier treatment if deterioration, if systemically unwell, if at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis), if mastoiditis present, or in children under 2 years of age with bilateral otitis media.

Amoxicillin¹

Consider co-amoxiclav if no improvement after 48 hours.

In severe infection, initial parenteral therapy with co-amoxiclav or cefuroxime.

Suggested duration of treatment 5 days (longer if severely ill)

If penicillin-allergic, clarithromycin²

Suggested duration of treatment 5 days (longer if severely ill)

Skin

Impetigo: small areas of skin infected

Seek local microbiology advice before using topical treatment in hospital.

Topical fusidic acid

Suggested duration of treatment 7 days is usually adequate (max. 10 days)

Alternative if meticillin-resistant Staphylococcus aureus, topical mupirocin

Suggested duration of treatment 7 days is usually adequate (max. 10 days)

1. Where amoxicillin is suggested ampicillin may be used

2. Where clarithromycin is suggested azithromycin or erythromycin may be used

Impetigo: widespread infection**Oral flucloxacillin**

If streptococci suspected in severe infection, add phenoxymethylpenicillin.

Suggested duration of treatment 7 days

*If penicillin-allergic, oral clarithromycin*¹

Suggested duration of treatment 7 days

Erysipelas**Phenoxymethylpenicillin or benzylpenicillin**

If severe infection, replace phenoxymethylpenicillin or benzylpenicillin with high-dose flucloxacillin; if meticillin-resistant *S. aureus* suspected, see section 5.1.1.2.

Suggested duration of treatment at least 7 days

*If penicillin-allergic, clindamycin or clarithromycin*¹

If meticillin-resistant *S. aureus* suspected in severe infection, see section 5.1.1.2.

Suggested duration of treatment at least 7 days

Cellulitis**Flucloxacillin (high dose)**

If streptococcal infection confirmed, replace flucloxacillin with phenoxymethylpenicillin or benzylpenicillin.

If Gram-negative bacteria or anaerobes suspected (e.g. facial infection, orbital infection, or infection caused by animal or human bites), use broad-spectrum antibacterials; if periumbilical cellulitis, use flucloxacillin + gentamicin.

If meticillin-resistant *S. aureus* suspected, see section 5.1.1.2

*If penicillin-allergic, clindamycin or clarithromycin*¹

If Gram-negative bacteria suspected, use broad-spectrum antibacterials.

If meticillin-resistant *S. aureus* suspected, see section 5.1.1.2

Staphylococcal scalded skin syndrome**Flucloxacillin**

Suggested duration of treatment 7–10 days

*If penicillin-allergic, clarithromycin*¹

Suggested duration of treatment 7–10 days

Animal and human bites

Cleanse wound thoroughly. For tetanus-prone wound, give human tetanus immunoglobulin (with a tetanus-containing vaccine if necessary, according to immunisation history and risk of infection), see under Tetanus Vaccines, section 14.4. Consider rabies prophylaxis (section 14.4) for bites from animals in endemic countries; assess risk of blood-borne viruses (including HIV, hepatitis B and C) and give appropriate prophylaxis to prevent viral spread.

Co-amoxiclav

If penicillin-allergic, clindamycin

Acne

See section 13.6.

Paronychia or 'septic spots' in neonate**Flucloxacillin**

If systemically unwell, add an aminoglycoside

Surgical wound infection

Flucloxacillin or co-amoxiclav

1. Where clarithromycin is suggested azithromycin or erythromycin may be used

Table 2. Summary of antibacterial prophylaxis**Prevention of recurrence of rheumatic fever**

Phenoxymethylpenicillin by mouth

Child 1 month–6 years 125 mg twice daily**Child 6–18 years** 250 mg twice daily

or

Erythromycin by mouth

Child 1 month–2 years 125 mg twice daily**Child 2–18 years** 250 mg twice daily**Prevention of secondary case of invasive group A streptococcal infection¹**

Phenoxymethylpenicillin by mouth

Neonate 12.5 mg/kg (max. 62.5 mg) every 6 hours for 10 days**Child 1 month–1 year** 62.5 mg every 6 hours for 10 days**Child 1–6 years** 125 mg every 6 hours for 10 days**Child 6–12 years** 250 mg every 6 hours for 10 days**Child 12–18 years** 250–500 mg every 6 hours for 10 days

If child penicillin allergic,

either erythromycin by mouth

Child 1 month–2 years 125 mg every 6 hours for 10 days**Child 2–8 years** 250 mg every 6 hours for 10 days**Child 8–18 years** 250–500 mg every 6 hours for 10 days or azithromycin by mouth [unlicensed indication]**Child 6 months–12 years** 12 mg/kg (max. 500 mg) once daily for 5 days**Child 12–18 years** 500 mg once daily for 5 days**Prevention of secondary case of meningococcal meningitis²**

Ciprofloxacin by mouth [unlicensed indication]

Neonate 30 mg/kg (max. 125 mg) as a single dose**Child 1 month–5 years** 30 mg/kg (max. 125 mg) as a single dose**Child 5–12 years** 250 mg as a single dose**Child 12–18 years** 500 mg as a single dose

or

Rifampicin by mouth

Neonate 5 mg/kg every 12 hours for 2 days**Child 1 month–1 year** 5 mg/kg every 12 hours for 2 days**Child 1–12 years** 10 mg/kg (max. 600 mg) every 12 hours for 2 days**Child 12–18 years** 600 mg every 12 hours for 2 days

or

1. For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Health Protection Agency Laboratory)

2. For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Health Protection Agency Laboratory). Unless there has been direct exposure of the mouth or nose to infectious droplets from a patient with meningococcal disease who has received less than 24 hours of antibacterial treatment, healthcare workers do not generally require chemoprophylaxis

Ceftriaxone by intramuscular injection [unlicensed indication]

Child 1 month–12 years 125 mg as a single dose**Child 12–18 years** 250 mg as a single dose**Prevention of secondary case of *Haemophilus influenzae* type b disease²**

Rifampicin by mouth

Child 1–3 months 10 mg/kg once daily for 4 days**Child 3 months–12 years** 20 mg/kg (max. 600 mg) once daily for 4 days**Child 12–18 years** 600 mg once daily for 4 days

or (if rifampicin cannot be used)

Ceftriaxone by intramuscular injection, or by intravenous injection, or by intravenous infusion [unlicensed indication]

Child 1 month–12 years 50 mg/kg (max. 1 g) once daily for 2 days; by intravenous infusion only**Child 12–18 years** 1 g once daily for 2 days

Within 4 weeks of illness onset in an index case with confirmed or suspected invasive *Haemophilus influenzae* type b disease, give antibacterial prophylaxis to all household contacts if there is a vulnerable individual in the household. Also, give antibacterial prophylaxis to the index case if they are in contact with vulnerable household contacts or if they are under 10 years of age. Vulnerable individuals include the immunocompromised, those with asplenia, or children under 10 years of age. If there are 2 or more cases of invasive *Haemophilus influenzae* type b disease within 120 days in a pre-school or primary school, antibacterial prophylaxis should also be given to all room contacts (including staff). For immunisation against *Haemophilus influenzae* type b disease, see section 14.4

Prevention of secondary case of diphtheria in non-immune patientErythromycin³ by mouth**Child 1 month–2 years** 125 mg every 6 hours for 7 days**Child 2–8 years** 250 mg every 6 hours for 7 days**Child 8–18 years** 500 mg every 6 hours for 7 days

Treat for further 10 days if nasopharyngeal swabs positive after first 7 days' treatment. For immunisation against diphtheria see section 14.4

Prevention of pertussisClarithromycin⁴ by mouth**Neonate** 7.5 mg/kg twice daily for 7 days**Child 1 month–12 years****Body-weight under 8 kg** 7.5 mg/kg twice daily for 7 days**Body-weight 8–11 kg** 62.5 mg twice daily for 7 days**Body-weight 12–19 kg** 125 mg twice daily for 7 days**Body-weight 20–29 kg** 187.5 mg twice daily for 7 days**Body-weight 30–40 kg** 250 mg twice daily for 7 days**Child 12–18 years** 500 mg twice daily for 7 days

Within 3 weeks of onset of cough in the index case, give antibacterial prophylaxis to all close contacts if amongst them there is at least one unimmunised or partially immunised child under 1 year of age, or if there is at least one individual who has not received a pertussis-containing vaccine more than 1 week and less than 5 years ago (so long as that individual lives or works with children under 4 months of age, is pregnant at over 32 weeks gestation, or is a healthcare worker who works with children under 1 year of age or with pregnant women). For immunisation against pertussis see section 14.4

3. Where erythromycin is suggested another macrolide (e.g. azithromycin or clarithromycin) may be used

4. Where clarithromycin is suggested azithromycin or erythromycin may be used

Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease

Phenoxymethylpenicillin by mouth

Child under 1 year 62.5 mg twice daily

Child 1–5 years 125 mg twice daily

Child 5–18 years 250 mg twice daily

If cover also needed for *H. influenzae* in child give amoxicillin instead

Child 1 month–5 years 125 mg twice daily

Child 5–12 years 250 mg twice daily

Child 12–18 years 500 mg twice daily

If penicillin-allergic, erythromycin by mouth

Child 1 month–2 years 125 mg twice daily

Child 2–8 years 250 mg twice daily

Child 8–18 years 500 mg twice daily

Note Antibacterial prophylaxis is not fully reliable; for vaccines in asplenia see p. 607. Antibacterial prophylaxis may be discontinued in children over 5 years of age with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection

Prevention of *Staphylococcus aureus* lung infection in cystic fibrosis

Primary prevention, flucloxacillin by mouth

Neonate 125 mg twice daily

Child 1 month–3 years 125 mg twice daily

Secondary prevention, flucloxacillin by mouth

Child 1 month–18 years 50 mg/kg (max. 1 g) twice daily

Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive¹

Isoniazid for 6 months

Neonate 10 mg/kg daily

Child 1 month–12 years 10 mg/kg daily (max. 300 mg daily)

Child 12–18 years 300 mg daily

or isoniazid + rifampicin for 3 months

Child 1 month–12 years isoniazid 10 mg/kg daily (max. 300 mg daily) + rifampicin 15 mg/kg daily (max. 450 mg daily if body-weight less than 50 kg; max. 600 mg daily if body-weight over 50 kg)

Child 12–18 years isoniazid 300 mg daily + rifampicin 600 mg daily (rifampicin 450 mg daily if body-weight less than 50 kg)

or (if isoniazid-resistant tuberculosis) rifampicin for 6 months

Child 1 month–12 years 15 mg/kg daily (max. 450 mg daily if body-weight less than 50 kg; max. 600 mg daily if body-weight over 50 kg)

Child 12–18 years 600 mg daily (450 mg daily if body-weight less than 50 kg)

1. For details of those who should receive chemoprophylaxis contact the lead clinician for local tuberculosis services (or a consultant in communicable disease control). See also section 5.1.9, for advice on immunocompromised patients and on prevention of tuberculosis

Prevention of urinary-tract infection

Trimethoprim by mouth

Neonate 2 mg/kg at night

Child 1 month–12 years 2 mg/kg (max. 100 mg) at night

or

Child 6 weeks–6 months 12.5 mg at night

Child 6 months–6 years 25 mg at night

Child 6–12 years 50 mg at night

Child 12–18 years 100 mg at night

or nitrofurantoin by mouth

Child 3 months–12 years 1 mg/kg at night

Child 12–18 years 50–100 mg at night

Antibacterial prophylaxis can be considered for recurrent infection, significant urinary-tract anomalies, or significant kidney damage. See also section 5.1.13

Prevention of infection from animal and human bites

Co-amoxiclav alone (or clindamycin if penicillin-allergic)

Cleanse wound thoroughly. For tetanus-prone wound, give human tetanus immunoglobulin (with a tetanus-containing vaccine if necessary, according to immunisation history and risk of infection), see under Tetanus vaccines, section 14.4. Consider rabies prophylaxis (section 14.4) for bites from animals in endemic countries. Assess risk of blood-borne viruses (including HIV, hepatitis B and C) and give appropriate prophylaxis to prevent viral spread. Antibacterial prophylaxis recommended for wounds less than 48–72 hours old when the risk of infection is high (e.g. bites from humans or cats; bites to the hand, foot, face, or genital area; bites involving oedema, crush or puncture injury, or other moderate to severe injury; wounds that cannot be debrided adequately; patients with diabetes mellitus, cirrhosis, asplenia, prosthetic joints or valves, or those who are immunocompromised). Give antibacterial prophylaxis for up to 5 days

Prevention of infection in gastro-intestinal procedures

Operations on stomach or oesophagus²

Single dose³ of i/v gentamicin or i/v cefuroxime or i/v co-amoxiclav

Add i/v teicoplanin⁴ if high risk of meticillin-resistant *Staphylococcus aureus*

Open biliary surgery²

Single dose³ of i/v cefuroxime + i/v metronidazole⁵ or i/v gentamicin + i/v metronidazole⁵ or i/v co-amoxiclav alone

Add i/v teicoplanin⁴ if high risk of meticillin-resistant *Staphylococcus aureus*

Resections of colon and rectum, and resections in inflammatory bowel disease, and appendectomy²

Single dose³ of i/v gentamicin + i/v metronidazole⁵ or i/v cefuroxime + i/v metronidazole⁵ or i/v co-amoxiclav alone

Add i/v teicoplanin⁴ if high risk of meticillin-resistant *Staphylococcus aureus*

2. Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure

3. Additional intra-operative or postoperative doses of antibacterial may be given for prolonged procedures or if there is major blood loss

4. Where teicoplanin is suggested vancomycin may be used

5. Metronidazole may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery

Endoscopic retrograde cholangiopancreatography¹

Single dose of i/v gentamicin *or* oral or i/v ciprofloxacin

Prophylaxis recommended if pancreatic pseudocyst, immunocompromised, history of liver transplantation, or risk of incomplete biliary drainage. For biliary complications following liver transplantation, add i/v amoxicillin or i/v teicoplanin²

Percutaneous endoscopic gastrostomy or jejunostomy¹

Single dose of i/v co-amoxiclav or i/v cefuroxime

Use single dose of i/v teicoplanin² if history of allergy to penicillins or cephalosporins, or if high risk of meticillin-resistant *Staphylococcus aureus*

Prevention of infection in orthopaedic surgery**Closed fractures¹**

Single dose³ of i/v cefuroxime *or* i/v flucloxacillin

If history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant *Staphylococcus aureus*, use single dose² of i/v teicoplanin⁴

Open fractures

i/v co-amoxiclav alone *or* i/v cefuroxime + i/v metronidazole (*or* i/v clindamycin alone if history of allergy to penicillins or to cephalosporins)

Add i/v teicoplanin² if high risk of meticillin-resistant *Staphylococcus aureus*. Start prophylaxis within 3 hours of injury and continue until soft tissue closure (max. 72 hours). At first debridement also use a single dose of i/v cefuroxime + i/v metronidazole + i/v gentamicin *or* i/v co-amoxiclav + i/v gentamicin (*or* i/v clindamycin + i/v gentamicin if history of allergy to penicillins or to cephalosporins).

At time of skeletal stabilisation and definitive soft tissue closure⁴ use a single dose of i/v gentamicin and i/v teicoplanin²

High lower-limb amputation¹

i/v co-amoxiclav alone *or* i/v cefuroxime + i/v metronidazole⁴

Continue antibacterial prophylaxis for at least 2 doses after procedure (max. duration of prophylaxis 5 days). If history of allergy to penicillin or to cephalosporins, or if high risk of meticillin-resistant *Staphylococcus aureus*, use i/v teicoplanin² + i/v gentamicin + i/v metronidazole⁴

Prevention of infection in obstetric surgery**Termination of pregnancy**

Single dose³ of oral metronidazole

If genital chlamydial infection cannot be ruled out, give doxycycline (section 5.1.3) postoperatively

Prevention of endocarditis**NICE guidance****Antimicrobial prophylaxis against infective endocarditis in children and adults undergoing interventional procedures (March 2008)**

Antibacterial prophylaxis and chlorhexidine mouthwash are **not** recommended for the prevention of endocarditis in patients undergoing dental procedures.

Antibacterial prophylaxis is **not** recommended for the prevention of endocarditis in patients undergoing procedures of the:

- upper and lower respiratory tract (including ear, nose, and throat procedures and bronchoscopy);
- genito-urinary tract (including urological, gynaecological, and obstetric procedures);
- upper and lower gastro-intestinal tract.

While these procedures can cause bacteraemia, there is no clear association with the development of infective endocarditis. Prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

Any infection in patients at risk of endocarditis⁵ should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

If patients at risk of endocarditis⁵ are undergoing a gastro-intestinal or genito-urinary tract procedure at a site where infection is suspected, they should receive appropriate antibacterial therapy that includes cover against organisms that cause endocarditis.

Patients at risk of endocarditis⁵ should be:

- advised to maintain good oral hygiene;
- told how to recognise signs of infective endocarditis, and advised when to seek expert advice.

Dermatological procedures

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who undergo dermatological procedures⁶ do not require antibacterial prophylaxis against endocarditis.

1. Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure

2. Where teicoplanin is suggested vancomycin may be used

3. Additional intra-operative or postoperative doses of antibacterial may be given for prolonged procedures or if there is major blood loss

4. Metronidazole may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery

5. Patients at risk of endocarditis include those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis

6. The British Association of Dermatologists Therapy Guidelines and Audit Subcommittee advise that such dermatological procedures include skin biopsies and excision of moles or of malignant lesions

Joint prostheses and dental treatment

Joint prostheses and dental treatment

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

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

Immunosuppression and indwelling intraperitoneal catheters

Immunosuppression and indwelling intraperitoneal catheters

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who are immunosuppressed (including transplant patients) and patients with indwelling intraperitoneal catheters do not require antibacterial prophylaxis for dental treatment provided there is no other indication for prophylaxis.

The Working Party has commented that there is little evidence that dental treatment is followed by infection in immunosuppressed and immunodeficient patients nor is there evidence that dental treatment is followed by infection in patients with indwelling intraperitoneal catheters.

a penicillin. Children who are allergic to one penicillin will be allergic to all because the hypersensitivity is related to the basic penicillin structure. As patients with a history of immediate hypersensitivity to penicillins may also react to the cephalosporins and other beta-lactam antibiotics, they should not receive these antibiotics; aztreonam may be less likely to cause hypersensitivity in penicillin-sensitive patients and can be used with caution. If a penicillin (or another beta-lactam antibiotic) is essential in a child with immediate hypersensitivity to penicillin then specialist advice should be sought on hypersensitivity testing or using a beta-lactam antibiotic with a different structure to the penicillin that caused the hypersensitivity (see also p. 270).

Individuals with a history of a minor rash (i.e. non-confluent, non-pruritic rash restricted to a small area of the body) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin and in these individuals a penicillin should not be withheld unnecessarily for serious infections; the possibility of an allergic reaction should, however, be borne in mind. Other beta-lactam antibiotics (including cephalosporins) can be used in these patients.

Other side effects A rare but serious toxic effect of the penicillins is encephalopathy due to cerebral irritation. This may result from excessively high doses or in patients with severe renal failure. The penicillins should not be given by intrathecal injection because they can cause encephalopathy which may be fatal.

Another problem relating to high doses of penicillin, or normal doses given to patients with renal failure, is the accumulation of electrolyte since most injectable penicillins contain either sodium or potassium.

Diarrhoea frequently occurs during oral penicillin therapy. It is most common with broad-spectrum penicillins, which can also cause antibiotic-associated colitis.

5.1.1 Penicillins

- 5.1.1.1 **Benzylpenicillin and phenoxymethylpenicillin**
- 5.1.1.2 **Penicillinase-resistant penicillins**
- 5.1.1.3 **Broad-spectrum penicillins**
- 5.1.1.4 **Antipseudomonal penicillins**
- 5.1.1.5 **Mecillinams**

The penicillins are bactericidal and act by interfering with bacterial cell wall synthesis. They diffuse well into body tissues and fluids, but penetration into the cerebrospinal fluid is poor except when the meninges are inflamed. They are excreted in the urine in therapeutic concentrations.

Hypersensitivity reactions The most important side-effect of the penicillins is hypersensitivity which causes rashes and anaphylaxis and can be fatal. Allergic reactions to penicillins occur in 1–10% of exposed individuals; anaphylactic reactions occur in fewer than 0.05% of treated patients. Individuals with a history of anaphylaxis, urticaria, or rash immediately after penicillin administration are at risk of immediate hypersensitivity to a penicillin; these individuals should not receive

5.1.1.1 Benzylpenicillin and phenoxymethylpenicillin

Benzylpenicillin (Penicillin G) remains an important and useful antibiotic but is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal), gonococcal, and meningococcal infections and also for anthrax (section 5.1.1.2), diphtheria, gas-gangrene, leptospirosis, and treatment of Lyme disease (section 5.1.1.3) in children. It is also used in combination with gentamicin for the empirical treatment of sepsis in neonates less than 48 hours old. Pneumococci, meningococci, and gonococci which have decreased sensitivity to penicillin have been isolated; **benzylpenicillin is no longer the drug of first choice for pneumococcal meningitis**. Although benzylpenicillin is effective in the treatment of tetanus, metronidazole (section 5.1.1.1) is preferred. Benzylpenicillin is inactivated by gastric acid and absorption from the gastro-intestinal tract is low; therefore it must be given by injection.

Benzathine benzylpenicillin or **procaine benzylpenicillin** is used in the treatment of syphilis (see Table 1 section 5.1); both are available from 'special-order' manufacturers or specialist importing companies, see p. 840.

Phenoxymethylpenicillin (Penicillin V) has a similar antibacterial spectrum to benzylpenicillin, but is less active. It is gastric acid-stable, so is suitable for oral administration. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable. It is indicated principally for respiratory-tract infections in children, for streptococcal tonsillitis, and for continuing treatment after one or more injections of benzylpenicillin when clinical response has begun. It should not be used for meningococcal or gonococcal infections. Phenoxymethylpenicillin is used for prophylaxis against streptococcal infections following rheumatic fever and against pneumococcal infections following splenectomy or in sickle cell disease.

Oral infections Phenoxymethylpenicillin is effective for dentoalveolar abscess.

BENZYLPENICILLIN SODIUM (Penicillin G)

Cautions history of allergy; false-positive urinary glucose (if tested for reducing substances); **interactions:** Appendix 1 (penicillins)

Contra-indications penicillin hypersensitivity

Renal impairment neurotoxicity—high doses may cause convulsions. Estimated glomerular filtration rate 10–50 mL/minute/1.73 m², use normal dose every 8–12 hours; estimated glomerular filtration rate less than 10 mL/minute/1.73 m² use normal dose every 12 hours

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk, but appropriate to use

Side-effects hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reactions; *rarely* CNS toxicity including convulsions (especially with high doses or in severe renal impairment), interstitial nephritis, haemolytic anaemia, leucopenia, thrombocytopenia and coagulation disorders; also reported diarrhoea (including antibiotic-associated colitis)

Indications and dose

Mild to moderate susceptible infections (including throat infections, otitis media, pneumonia, cellulitis, neonatal sepsis, Table 1, section 5.1)

- By intramuscular injection or by slow intravenous injection or infusion (intravenous route recommended in neonates and infants)

Neonate under 7 days 25 mg/kg every 12 hours; increased to 25 mg/kg every 8 hours if necessary

Neonate 7–28 days 25 mg/kg every 8 hours; dose doubled in severe infection

Child 1 month–18 years 25 mg/kg every 6 hours; increased to 50 mg/kg every 4–6 hours (max. 2.4 g every 4 hours) in severe infection

Endocarditis (combined with another antibacterial if necessary, see Table 1, section 5.1)

- By slow intravenous injection or infusion

Child 1 month–18 years 25 mg/kg every 4 hours, increased if necessary to 50 mg/kg (max. 2.4 g) every 4 hours

Meningitis, meningococcal disease

- By intravenous infusion

Neonate under 7 days 50 mg/kg every 12 hours

Neonate 7–28 days 50 mg/kg every 8 hours

Child 1 month–18 years 50 mg/kg every 4–6 hours (max. 2.4 g every 4 hours)

Important. If meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) is suspected, a single dose of benzylpenicillin should be given before transferring the child to hospital urgently, so long as this does not delay the transfer. If a child with suspected bacterial meningitis without non-blanching rash cannot be transferred to hospital urgently, a single dose of benzylpenicillin should be given before the transfer. Suitable doses of benzylpenicillin by intravenous injection (or by intramuscular injection) are: **Infant under 1 year** 300 mg; **Child 1–9 years** 600 mg, **10 years and over** 1.2 g. In penicillin allergy, cefotaxime (section 5.1.2) may be an alternative; chloramphenicol (section 5.1.7) may be used if there is a history of anaphylaxis to penicillins

Administration Intravenous route recommended in neonates and infants. For *intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%; give over 15–30 minutes. Longer administration time is particularly important when using doses of 50 mg/kg (or greater) to avoid CNS toxicity

Safe practice

Intrathecal injection of benzylpenicillin is **not recommended**

Crystapen® (Genus) [PoM]

Injection, powder for reconstitution, benzylpenicillin sodium (unbuffered), net price 600-mg vial = 95p, 2-val 'GP pack' = £2.64; 1.2-g vial = £1.89
Electrolytes Na⁺ 1.68 mmol/600-mg vial; 3.36 mmol/1.2-g vial

PHENOXYMETHYL PENICILLIN (Penicillin V)

Cautions see under Benzylpenicillin; **interactions:** Appendix 1 (penicillins)

Contra-indications see under Benzylpenicillin

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk, but appropriate to use

Side-effects see under Benzylpenicillin

Indications and dose

Susceptible infections including oral infections, tonsillitis, otitis media, erysipelas, cellulitis

- By mouth

Child 1 month–1 year 62.5 mg 4 times daily (increased up to 12.5 mg/kg 4 times daily if necessary)

Child 1–6 years 125 mg 4 times daily (increased up to 12.5 mg/kg 4 times daily if necessary)

Child 6–12 years 250 mg 4 times daily (increased up to 12.5 mg/kg 4 times daily if necessary)

Child 12–18 years 500 mg 4 times daily (increased up to 1 g 4 times daily if necessary)

Prevention of pneumococcal infection in asplenia or sickle cell disease, see Table 2, section 5.1

Prevention of recurrence of rheumatic fever, see Table 2, section 5.1

Prevention of group A streptococcal infection, see Table 2, section 5.1

Phenoxymethylpenicillin (Non-proprietary) (PoM)

Tablets, phenoxymethylpenicillin (as potassium salt) 250 mg, net price 28-tab pack = £1.14. Label: 9, 23

Dental prescribing on NHS Phenoxymethylpenicillin Tablets may be prescribed

Oral solution, phenoxymethylpenicillin (as potassium salt) for reconstitution with water, net price 125 mg/5 mL, 100 mL = £14.73; 250 mg/5 mL, 100 mL = £14.66. Label: 9, 23

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Phenoxymethylpenicillin Oral Solution may be prescribed

5.1.1.2 Penicillinase-resistant penicillins

Most staphylococci are now resistant to benzylpenicillin because they produce penicillinases. **Flucloxacillin**, however, is not inactivated by these enzymes and is thus effective in infections caused by penicillin-resistant staphylococci, which is the main indication for its use. Flucloxacillin is acid-stable and can, therefore, be given by mouth as well as by injection.

Flucloxacillin is well absorbed from the gut. For a warning on hepatic disorders see under Flucloxacillin.

MRSA Infection from *Staphylococcus aureus* strains resistant to meticillin [now discontinued] (meticillin-resistant *Staph. aureus*, MRSA) and to flucloxacillin can be difficult to manage. Treatment is guided by the sensitivity of the infecting strain.

Rifampicin (section 5.1.9) or **sodium fusidate** (section 5.1.7) should not be used alone because resistance may develop rapidly. **Clindamycin** alone or a combination of rifampicin and sodium fusidate can be used for *skin and soft-tissue infections* caused by MRSA; a **tetracycline** is an alternative in children over 12 years of age. A **glycopeptide** (e.g. vancomycin, section 5.1.7) can be used for severe skin and soft-tissue infections associated with MRSA. A combination of a glycopeptide and sodium fusidate or a glycopeptide and rifampicin can be considered for skin and soft-tissue infections that have failed to respond to a single antibacterial. **Linezolid** (section 5.1.7) should be reserved for skin and soft-tissue infections that have not responded to other antibacterials or for children who cannot tolerate other antibacterials.

A **glycopeptide** can be used for *pneumonia* associated with MRSA. **Linezolid** should be reserved for hospital-acquired pneumonia that has not responded to other antibacterials or for children who cannot tolerate other antibacterials.

Trimethoprim or **nitrofurantoin** can be used for *urinary-tract infections* caused by MRSA; a **tetracycline** is an alternative in children over 12 years of age. A **glycopeptide** can be used for urinary-tract infections that are severe or resistant to other antibacterials.

A **glycopeptide** can be used for *septicaemia* associated with MRSA.

For the management of endocarditis, osteomyelitis, or septic arthritis associated with MRSA, see Table 1, section 5.1.

Prophylaxis with vancomycin or teicoplanin (alone or in combination with another antibacterial active against

other pathogens) is appropriate for patients undergoing surgery if:

- there is a history of MRSA colonisation or infection without documented eradication;
- there is a risk that the patient's MRSA carriage has recurred;
- the patient comes from an area with a high prevalence of MRSA.

It is important that hospitals have infection control guidelines to minimise MRSA transmission, including policies on isolation and treatment of MRSA carriers and on hand hygiene. For eradication of nasal carriage of MRSA, see section 12.2.3.

FLUCLOXACILLIN

Cautions see under Benzylpenicillin (section 5.1.1.1); risk of kernicterus in jaundiced neonates when high doses given parenterally; **interactions:** Appendix 1 (penicillins)

Hepatic disorders

Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors. Healthcare professionals are reminded that:

- flucloxacillin should not be used in patients with a history of hepatic dysfunction associated with flucloxacillin;
- flucloxacillin should be used with caution in patients with hepatic impairment;
- careful enquiry should be made about hypersensitivity reactions to beta-lactam antibacterials.

Contra-indications see under Benzylpenicillin (section 5.1.1.1)

Hepatic impairment see Cautions and Hepatic Disorders above

Renal impairment use normal dose every 8 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk, but appropriate to use

Side-effects see under Benzylpenicillin (section 5.1.1.1); also gastro-intestinal disturbances; very rarely hepatitis and cholestatic jaundice reported (see also Hepatic Disorders above)

Indications and dose

Infections due to beta-lactamase-producing staphylococci including otitis externa; adjunct in pneumonia, impetigo, cellulitis

- By mouth

Neonate under 7 days 25 mg/kg twice daily

Neonate 7–21 days 25 mg/kg 3 times daily

Neonate 21–28 days 25 mg/kg 4 times daily

Child 1 month–2 years 62.5–125 mg 4 times daily

Child 2–10 years 125–250 mg 4 times daily

Child 10–18 years 250–500 mg 4 times daily

- By intramuscular injection

Child 1 month–18 years 12.5–25 mg/kg every 6 hours (max. 500 mg every 6 hours)

- By slow intravenous injection or by intravenous infusion

Neonate under 7 days 25 mg/kg every 12 hours; may be doubled in severe infection

Neonate 7–21 days 25 mg/kg every 8 hours; may be doubled in severe infection

Neonate 21–28 days 25 mg/kg every 6 hours; may be doubled in severe infection

Child 1 month–18 years 12.5–25 mg/kg every 6 hours (max. 1 g every 6 hours); may be doubled in severe infection

Osteomyelitis (Table 1, section 5.1), cerebral abscess, staphylococcal meningitis

- By slow intravenous injection or by intravenous infusion

Neonate under 7 days 50–100 mg/kg every 12 hours

Neonate 7–21 days 50–100 mg/kg every 8 hours

Neonate 21–28 days 50–100 mg/kg every 6 hours

Child 1 month–18 years 50 mg/kg (max. 2 g) every 6 hours

Endocarditis (Table 1, section 5.1)

- By slow intravenous injection or by intravenous infusion

Child 1 month–18 years 50 mg/kg (max. 2 g) every 6 hours

Prevention of staphylococcal lung infection in cystic fibrosis

Table 2, section 5.1

Staphylococcal lung infection in cystic fibrosis

- By mouth

Child 1 month–18 years 25 mg/kg (max. 1 g) 4 times daily; total daily dose may alternatively be given in 3 divided doses

- By slow intravenous injection or by intravenous infusion

Child 1 month–18 years 50 mg/kg (max. 2 g) every 6 hours

Administration for intermittent intravenous infusion, dilute reconstituted solution in Glucose 5% or Sodium Chloride 0.9% and give over 30–60 minutes

Flucloxacillin (Non-proprietary) (POM)

Capsules, flucloxacillin (as sodium salt) 250 mg, net price 28 = £1.57; 500 mg, 28 = £2.23. Label: 9, 23
Brands include Floxapen[®], Fluclomix[®], Ladropen[®]

Oral solution (= elixir or syrup), flucloxacillin (as sodium salt) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £21.38; 250 mg/5 mL, 100 mL = £26.04. Label: 9, 23

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Injection, powder for reconstitution, flucloxacillin (as sodium salt). Net price 250-mg vial = £1.23; 500-mg vial = £2.45; 1-g vial = £4.90

5.1.1.3 Broad-spectrum penicillins

Ampicillin is active against certain Gram-positive and Gram-negative organisms but is inactivated by penicillinases including those produced by *Staphylococcus*

aureus and by common Gram-negative bacilli such as *Escherichia coli*. Ampicillin is also active against *Listeria* spp. and enterococci. Almost all staphylococci, approx. 60% of *E. coli* strains and approx. 20% of *Haemophilus influenzae* strains are now resistant. The likelihood of resistance should therefore be considered before using ampicillin for the 'blind' treatment of infections; in particular, it should not be used for hospital patients without checking sensitivity.

Ampicillin can be given by mouth, but less than half the dose is absorbed and absorption is further decreased by the presence of food in the gut. Ampicillin is well excreted in the bile and urine.

Amoxicillin is a derivative of ampicillin and has a similar antibacterial spectrum. It is better absorbed than ampicillin when given by mouth, producing higher plasma and tissue concentrations; unlike ampicillin, absorption is not affected by the presence of food in the stomach.

Amoxicillin or ampicillin are principally indicated for the treatment of community-acquired pneumonia and middle ear infections, both of which may be due to *Streptococcus pneumoniae* and *H. influenzae*, and for urinary-tract infections (section 5.1.13). They are also used in the treatment of endocarditis and listerial meningitis. Amoxicillin may also be used for the treatment of Lyme disease [not licensed], see below.

Maculopapular rashes occur commonly with ampicillin (and amoxicillin) but are not usually related to true penicillin allergy. They often occur in children with glandular fever; broad-spectrum penicillins should not therefore be used for 'blind' treatment of a sore throat. The risk of rash is also increased in children with acute or chronic lymphocytic leukaemia or in cytomegalovirus infection.

Co-amoxiclav consists of amoxicillin with the beta-lactamase inhibitor clavulanic acid. Clavulanic acid itself has no significant antibacterial activity but, by inactivating beta-lactamases, it makes the combination active against beta-lactamase-producing bacteria that are resistant to amoxicillin. These include resistant strains of *Staph. aureus*, *E. coli*, and *H. influenzae*, as well as many *Bacteroides* and *Klebsiella* spp. Co-amoxiclav should be reserved for infections likely, or known, to be caused by amoxicillin-resistant beta-lactamase-producing strains.

A combination of ampicillin with flucloxacillin (as co-fluampicil) is available to treat infections involving either streptococci or staphylococci (e.g. cellulitis).

Lyme disease Lyme disease should generally be treated by those experienced in its management. **Amoxicillin** [unlicensed indication], **cefuroxime axetil** or **doxycycline** are the antibacterials of choice for early Lyme disease or Lyme arthritis but doxycycline should only be used in children over 12 years of age. If these antibacterials are contra-indicated, a **macrolide** (e.g. clarithromycin) can be used for early Lyme disease. Intravenous administration of **ceftriaxone**, **cefotaxime** (section 5.1.2.1), or **benzylpenicillin** (p. 262) is recommended for Lyme disease associated with cardiac or neurological complications. The duration of treatment is usually 2–4 weeks; Lyme arthritis may require further treatment.

Oral infections Amoxicillin is as effective as phenoxymethylpenicillin (section 5.1.1.1) but is better absorbed; however, it may encourage emergence of resistant organisms.

Like phenoxymethylpenicillin, amoxicillin is ineffective against bacteria that produce beta-lactamases. Co-amoxiclav is active against beta-lactamase-producing bacteria that are resistant to amoxicillin. Co-amoxiclav may be used for severe dental infection with spreading cellulitis or dental infection not responding to first-line antibacterial treatment.

AMOXICILLIN (Amoxycillin)

Cautions see under Ampicillin; maintain adequate hydration with high doses (particularly during parenteral therapy); **interactions:** Appendix 1 (penicillins)

Contra-indications see under Ampicillin

Renal impairment risk of crystalluria with high doses (particularly during parenteral therapy). Reduce dose in severe impairment; rashes more common

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk, but appropriate to use

Side-effects see under Ampicillin

Indications and dose

Susceptible infections including urinary-tract infections, sinusitis, otitis media (but see Table 1, section 5.1), uncomplicated community-acquired pneumonia, oral infections (Table 1, section 5.1), Lyme disease (see notes above), salmonellosis, cystic fibrosis (treatment of asymptomatic *Haemophilus influenzae* carriage or mild exacerbation)

• By mouth

Neonate 7–28 days 30 mg/kg (max. 125 mg) 3 times daily

Child 1 month–1 year 125 mg 3 times daily; increased if necessary up to 30 mg/kg 3 times daily

Child 1–5 years 250 mg 3 times daily; increased if necessary up to 30 mg/kg 3 times daily

Child 5–12 years 500 mg 3 times daily; increased if necessary up to 30 mg/kg (max. 1 g) 3 times daily

Child 12–18 years 500 mg 3 times daily; in severe infection 1 g 3 times daily

• By intravenous injection or infusion

Neonate under 7 days 30 mg/kg every 12 hours; dose doubled in severe infection, community-acquired pneumonia, or salmonellosis

Neonate 7–28 days 30 mg/kg every 8 hours; dose doubled in severe infection, community-acquired pneumonia, or salmonellosis

Child 1 month–18 years 20–30 mg/kg (max. 500 mg) every 8 hours; dose doubled in severe infection (max. 4 g daily)

Listerial meningitis (in combination with another antibacterial, Table 1, section 5.1), group B streptococcal infection, enterococcal endocarditis (in combination with another antibiotic)

• By intravenous infusion

Neonate under 7 days 50 mg/kg every 12 hours; dose may be doubled in meningitis

Neonate 7–28 days 50 mg/kg every 8 hours; dose may be doubled in meningitis

Child 1 month–18 years 50 mg/kg every 4–6 hours (max. 2 g every 4 hours)

***Helicobacter pylori* eradication** section 1.3

Note Amoxicillin doses in BNFC may differ from those in product literature

Administration Displacement value may be significant when reconstituting injection, consult local guidelines. Dilute intravenous injection to a concentration of 50 mg/mL (100 mg/mL for neonates). May be further diluted with Glucose 5% or Glucose 10% or Sodium chloride 0.9% or 0.45% for intravenous infusion. Give intravenous infusion over 30 minutes when using doses over 30 mg/kg

Amoxicillin (Non-proprietary) (PoM)

Capsules, amoxicillin (as trihydrate) 250 mg, net price 21 = £1.37; 500 mg, 21 = £1.61. Label: 9

Brands include Amix®, Amoram®, Amoxident®, Galenamox®, Rimoxallin®

Dental prescribing on NHS Amoxicillin Capsules may be prescribed

Oral suspension, amoxicillin (as trihydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £1.09; 250 mg/5 mL, 100 mL = £1.29. Label: 9

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Brands include Amoram®, Galenamox®, Rimoxallin®

Dental prescribing on NHS Amoxicillin Oral Suspension may be prescribed

Injection, powder for reconstitution, amoxicillin (as sodium salt), net price 250-mg vial = 32p; 500-mg vial = 55p; 1-g vial = £1.10

Amoxit® (GSK) (PoM)

Capsules, both maroon/gold, amoxicillin (as trihydrate), 250 mg, net price 21-cap pack = £3.38; 500 mg, 21-cap pack = £6.77. Label: 9

Paediatric suspension, amoxicillin 125 mg (as trihydrate)/1.25 mL when reconstituted with water, net price 20 mL (peach- strawberry- and lemon-flavoured) = £3.18. Label: 9, counselling, use of pipette

Excipients include sucrose 600 mg/1.25 mL

Injection, powder for reconstitution, amoxicillin (as sodium salt), net price 500-mg vial = 55p; 1-g vial = £1.10

Electrolytes Na⁺ 3.3 mmol/g

AMPICILLIN

Cautions history of allergy; erythematous rashes common in glandular fever (see notes above); increased risk of erythematous rashes in cyto-

megalovirus infection, and acute or chronic lymphocytic leukaemia (see notes above); **interactions:** Appendix 1 (penicillins)

Contra-indications penicillin hypersensitivity

Renal impairment if estimated glomerular filtration rate less than 10 mL/minute/1.73 m² reduce dose or frequency—rashes more common

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk, but appropriate to use

Side-effects nausea, vomiting, diarrhoea; rashes (discontinue treatment); rarely, antibiotic-associated colitis; see also under Benzylpenicillin (section 5.1.1.1)

Indications and dose

Susceptible infections including urinary-tract infections, otitis media, sinusitis, uncomplicated community-acquired pneumonia (Table 1, section 5.1), salmonellosis

• By mouth

Neonate 7–21 days 30 mg/kg (max. 125 mg) 3 times daily

Neonate 21–28 days 30 mg/kg (max. 125 mg) 4 times daily

Child 1 month–1 year 125 mg 4 times daily; increased if necessary up to 30 mg/kg 4 times daily

Child 1–5 years 250 mg 4 times daily; increased if necessary up to 30 mg/kg 4 times daily

Child 5–12 years 500 mg 4 times daily; increased if necessary up to 30 mg/kg (max. 1 g) 4 times daily

Child 12–18 years 500 mg 4 times daily; in severe infection 1 g 4 times daily

• By intravenous injection or infusion

Neonate under 7 days 30 mg/kg every 12 hours; dose doubled in severe infection, community-acquired pneumonia, or salmonellosis

Neonate 7–21 days 30 mg/kg every 8 hours; dose doubled in severe infection, community-acquired pneumonia, or salmonellosis

Neonate 21–28 days 30 mg/kg every 6 hours; dose doubled in severe infection, community-acquired pneumonia, or salmonellosis

Child 1 month–18 years 25 mg/kg (max. 500 mg) every 6 hours; dose doubled in severe infection

Listerial meningitis, group B streptococcal infection, enterococcal endocarditis (in combination with another antibacterial, see Table 1, section 5.1)

• By intravenous infusion

Neonate under 7 days 50 mg/kg every 12 hours; dose doubled in meningitis

Neonate 7–21 days 50 mg/kg every 8 hours; dose doubled in meningitis

Neonate 21–28 days 50 mg/kg every 6 hours; dose doubled in meningitis

Child 1 month–18 years 50 mg/kg every 4–6 hours (max. 2 g every 4 hours)

Administration *Oral*: administer at least 30 minutes before food

Injection: displacement value may be significant when reconstituting injection, consult local guidelines. Dilute intravenous injection to a concentration of 50–100 mg/mL. May be further diluted with glucose 5% or 10% or sodium chloride 0.9% or 0.45% for infusion. Give over 30 minutes when using doses of greater than 50 mg/kg to avoid CNS toxicity including convulsions.

Ampicillin (Non-proprietary) (PoM)

Capsules, ampicillin 250 mg, net price 28 = £4.75; 500 mg, 28 = £21.37. Label: 9, 23

Brands include Rimacillin®

Oral suspension, ampicillin 125 mg/5 mL when reconstituted with water, net price 100 mL = £7.88; 250 mg/5 mL, 100 mL = £11.84. Label: 9, 23

Brands include Rimacillin®

Injection, powder for reconstitution, ampicillin (as sodium salt), net price 500-mg vial = £7.83

Penbritin® (Chemidex) (PoM)

Capsules, both grey/red, ampicillin (as trihydrate) 250 mg, net price 28-cap pack = £2.10; 500 mg, 28-cap pack = £5.28. Label: 9, 23

Syrup, apricot- caramel- and peppermint-flavoured, ampicillin (as trihydrate) for reconstitution with water, 250 mg/5 mL, net price 100 mL = £11.84. Label: 9, 23

Excipients include sucrose 3.6 g/5 mL

With flucloxacillin

Co-fluampicil (Non-proprietary) (PoM)

Capsules, co-fluampicil 250/250 (flucloxacillin 250 mg as sodium salt, ampicillin 250 mg as trihydrate), net price 28-cap pack = £3.29. Label: 9, 22

Brands include Flu-Amp®

Syrup, co-fluampicil 125/125 (flucloxacillin 125 mg as magnesium salt, ampicillin 125 mg as trihydrate)/5 mL when reconstituted with water, net price 100 mL = £22.86. Label: 9, 22

Magnapen® (Wockhardt) (PoM)

Injection 500 mg, powder for reconstitution, co-flu-ampicil 250/250 (flucloxacillin 250 mg as sodium salt, ampicillin 250 mg as sodium salt), net price per vial = £1.33

Electrolytes Na⁺ 1.3 mmol/vial

CO-AMOXICLAV

A mixture of amoxicillin (as the trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate); the proportions are expressed in the form *x/y* where *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively

Cautions see under Ampicillin and notes above; maintain adequate hydration with high doses (particularly during parenteral therapy); **interactions**: Appendix 1 (penicillins)

Cholestatic jaundice Cholestatic jaundice can occur either during or shortly after the use of co-amoxiclav. An epidemiological study has shown that the risk of acute liver toxicity was about 6 times greater with co-amoxiclav than with amoxicillin; these reactions have only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal. The duration of treatment should be appropriate to the indication and should not usually exceed 14 days

Contra-indications penicillin hypersensitivity, history of co-amoxiclav-associated or penicillin-associated jaundice or hepatic dysfunction

Hepatic impairment monitor liver function in liver disease. See also Cholestatic Jaundice above

Renal impairment risk of crystalluria with high doses (particularly during parenteral therapy).

Co-amoxiclav 125/31 suspension, 250/62 suspension, 250/125 tablets, or 500/125 tablets: use normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m². Use the normal dose

recommended for mild or moderate infections every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

Co-amoxiclav 400/57 suspension: avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

Co-amoxiclav injection: use normal initial dose and then use half normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; use normal initial dose and then use half normal dose every 24 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk, but appropriate to use

Side-effects see under Ampicillin; hepatitis, cholestatic jaundice (see above); Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, vasculitis reported; rarely prolongation of bleeding time, dizziness, headache, convulsions (particularly with high doses or in renal impairment); superficial staining of teeth with suspension, phlebitis at injection site

Indications and dose

Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis, animal bites

- By mouth, expressed as co-amoxiclav (see also under Other Oral Preparations below)

Neonate 0.25 mL/kg of 125/31 suspension 3 times daily

Child 1 month–1 year 0.25 mL/kg of 125/31 suspension 3 times daily; dose doubled in severe infection

Child 1–6 years 5 mL of 125/31 suspension 3 times daily or 0.25 mL/kg of 125/31 suspension 3 times daily; dose doubled in severe infection

Child 6–12 years 5 mL of 250/62 suspension 3 times daily or 0.15 mL/kg of 250/62 suspension 3 times daily; dose doubled in severe infection

Child 12–18 years one 250/125 strength tablet 3 times daily; increased in severe infections to one 500/125 strength tablet 3 times daily

- By intravenous injection over 3–4 minutes or by intravenous infusion, expressed as co-amoxiclav

Neonate 30 mg/kg every 12 hours

Child 1–3 months 30 mg/kg every 12 hours

Child 3 months–18 years 30 mg/kg (max. 1.2 g) every 8 hours

Severe dental infection with spreading cellulitis or dental infection not responding to first-line antibacterial, see notes above

- By mouth, expressed as co-amoxiclav

Child 12–18 years one 250/125 strength tablet every 8 hours for 5 days

Administration for intermittent intravenous infusion dilute reconstituted solution to a concentration of 10 mg/mL with Sodium Chloride 0.9%; give over 30–40 minutes

Co-amoxiclav (Non-proprietary) (PoM)

Tablets, co-amoxiclav 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £2.62. Label: 9

Dental prescribing on NHS Co-amoxiclav 250/125 Tablets may be prescribed

Tablets, co-amoxiclav 500/125 (amoxicillin 500 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £4.13. Label: 9

Oral suspension, co-amoxiclav 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31.25 mg as potassium salt)/5 mL when reconstituted with water, net price 100 mL = £1.63. Label: 9

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Co-amoxiclav 125/31 Suspension may be prescribed

Oral suspension, co-amoxiclav 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62.5 mg as potassium salt)/5 mL when reconstituted with water, net price 100 mL = £1.72. Label: 9

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Co-amoxiclav 250/62 Suspension may be prescribed

Injection 500/100, powder for reconstitution, co-amoxiclav 500/100 (amoxicillin 500 mg as sodium salt, clavulanic acid 100 mg as potassium salt), net price per vial = £1.21

Injection 1000/200, powder for reconstitution, co-amoxiclav 1000/200 (amoxicillin 1 g as sodium salt, clavulanic acid 200 mg as potassium salt), net price per vial = £2.62

Augmentin® (GSK) (PoM)

Tablets 375 mg, f/c, co-amoxiclav 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £4.19. Label: 9

Tablets 625 mg, f/c, co-amoxiclav 500/125 (amoxicillin 500 mg as trihydrate, clavulanic acid 125 mg as potassium salt). Net price 21-tab pack = £8.00. Label: 9

Suspension '125/31 SF', sugar-free, co-amoxiclav 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31.25 mg as potassium salt)/5 mL when reconstituted with water. Net price 100 mL (raspberry- and orange-flavoured) = £2.95. Label: 9

Excipients include aspartame 12.5 mg/5 mL (section 9.4.1)

Suspension '250/62 SF', sugar-free, co-amoxiclav 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62.5 mg as potassium salt)/5 mL when reconstituted with water. Net price 100 mL (raspberry- and orange-flavoured) = £3.00. Label: 9

Excipients include aspartame 12.5 mg/5 mL (section 9.4.1)

Injection 600 mg, powder for reconstitution, co-amoxiclav 500/100 (amoxicillin 500 mg as sodium salt, clavulanic acid 100 mg as potassium salt). Net price per vial = £1.06

Electrolytes Na⁺ 1.35 mmol, K⁺ 0.5 mmol/600-mg vial

Injection 1.2 g, powder for reconstitution, co-amoxiclav 1000/200 (amoxicillin 1 g as sodium salt, clavulanic acid 200 mg as potassium salt). Net price per vial = £1.06

Electrolytes Na⁺ 2.7 mmol, K⁺ 1 mmol/1.2-g vial

Other oral preparations

Co-amoxiclav (Non-proprietary) (PoM)

Suspension '400/57', co-amoxiclav 400/57 (amoxicillin 400 mg as trihydrate, clavulanic acid 57 mg as potassium salt)/5 mL when reconstituted with water. Net price 35 mL = £4.13, 70 mL = £5.79. Label: 9

Excipients may include aspartame (section 9.4.1)

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Brands include *Augmentin-Duo*®

Dose

Child 2 months–2 years 0.15 mL/kg twice daily, doubled in severe infection

Child 2–6 years (13–21 kg) 2.5 mL twice daily, doubled in severe infection

Child 7–12 years (22–40 kg) 5 mL twice daily, doubled in severe infection

Child 12–18 years (over 40 kg) 10 mL twice daily, increased to 10 mL three times daily in severe infection

5.1.1.4 Antipseudomonal penicillins

Piperacillin, a ureidopenicillin, is only available in combination with the beta-lactamase inhibitor tazobactam. **Ticarcillin**, a carboxypenicillin, is only available in combination with the beta-lactamase inhibitor clavulanic acid (section 5.1.1.3). Both preparations have a broad spectrum of activity against a range of Gram-positive and Gram-negative bacteria, and anaerobes. Piperacillin with tazobactam has activity against a wider range of Gram-negative organisms than ticarcillin with clavulanic acid and it is more active against *Pseudomonas aeruginosa*. These antibacterials are not active against MRSA.

These antipseudomonal penicillins are used in the treatment of septicaemia, hospital-acquired pneumonia, complicated infections involving the urinary-tract, skin and soft-tissue or intra-abdomen. They may be used for the empirical treatment of septicaemia in immunocompromised children but otherwise should generally be reserved for serious infections resistant to other antibacterials. For severe pseudomonas infections these antipseudomonal penicillins can be given with an aminoglycoside (e.g. gentamicin, section 5.1.4) since they have a synergistic effect.

Piperacillin with tazobactam is used in cystic fibrosis for the treatment of *Ps. aeruginosa* colonisation when ciprofloxacin and nebulised colistimethate sodium have been ineffective; it can also be used in infective exacerbations, when it is combined with an aminoglycoside.

Owing to the sodium content of many of these antibiotics, high doses may lead to hypernatraemia.

PIPERACILLIN WITH TAZOBACTAM

Cautions see under Benzylpenicillin (section 5.1.1.1); interactions: Appendix 1 (penicillins)

Contra-indications see under Benzylpenicillin (section 5.1.1.1)

Renal impairment dose expressed as a combination of piperacillin and tazobactam (both as sodium salts). **Child under 12 years** 78.75 mg/kg (max. 4.5 g) every 8 hours if estimated glomerular filtration rate less than 50 mL/minute/1.73 m². **Child 12–18 years** max. 4.5 g every 8 hours if estimated glomerular filtration rate 20–40 mL/minute/1.73 m²; max. 4.5 g every 12 hours if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding trace amounts in milk, but appropriate to use

Side-effects see under Benzylpenicillin (section 5.1.1.1); also nausea, vomiting, diarrhoea; *less commonly* stomatitis, dyspepsia, constipation, jaundice, hypotension, headache, insomnia, injection-site reactions; *rarely* abdominal pain, hepatitis, eosinophilia; *very rarely* hypoglycaemia, hypokalaemia, pancytopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis

Licensed use not licensed for use in children under 12 years (except for children 2–12 years with neutropenia and complicated intra-abdominal infections)

Indications and dose

Expressed as a combination of piperacillin and tazobactam (both as sodium salts) in a ratio of 8:1

Hospital-acquired pneumonia, septicaemia, complicated infections involving the urinary-tract or skin and soft tissues

• By intravenous infusion

Neonate 90 mg/kg every 8 hours

Child 1 month–12 years 90 mg/kg every 6–8 hours; (max 4.5 g every 6 hours)

Child 12–18 years 4.5 g every 8 hours, increased to 4.5 g every 6 hours in severe infections

Infections in children with neutropenia

• By intravenous infusion

Child 1 month–18 years 90 mg/kg (max. 4.5 g) every 6 hours

Complicated intra-abdominal infections

• By intravenous infusion

Child 2–12 years 112.5 mg/kg (max. 4.5 g) every 8 hours

Child 12–18 years 4.5 g every 8 hours, increased to 4.5 g every 6 hours in severe infection

Administration displacement value may be significant when reconstituting injection, consult local guidelines. For *intravenous infusion*, dilute reconstituted solution to a concentration of 15–90 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 30 minutes

Piperacillin with tazobactam (Non-proprietary) (PoM)

Injection 2.25 g, powder for reconstitution, piperacillin 2 g (as sodium salt), tazobactam 250 mg (as sodium salt), net price 2.25-g vial = £3.10

Injection 4.5 g, powder for reconstitution, piperacillin 4 g (as sodium salt), tazobactam 500 mg (as sodium salt), net price 4.5-g vial = £12.90

Tazocin® (Pfizer) (PoM)

Injection 2.25 g, powder for reconstitution, piperacillin 2 g (as sodium salt), tazobactam 250 mg (as sodium salt), net price 2.25-g vial = £7.65

Electrolytes Na⁺ 5.58 mmol/2.25-g vial

Injection 4.5 g, powder for reconstitution, piperacillin 4 g (as sodium salt), tazobactam 500 mg (as sodium salt), net price 4.5-g vial = £15.17

Electrolytes Na⁺ 11.16 mmol/4.5-g vial

TICARCILLIN WITH CLAVULANIC ACID

Cautions see under Benzylpenicillin (section 5.1.1.1); **interactions:** Appendix 1 (penicillins)

Cholestatic jaundice For a warning on cholestatic jaundice possibly associated with clavulanic acid, see under Co-amoxiclav

Contra-indications see under Benzylpenicillin (section 5.1.1.1)

Hepatic impairment manufacturer advises caution in severe impairment; also cholestatic jaundice, see under Co-amoxiclav

Renal impairment **Neonate** reduce dose if estimated glomerular filtration rate less than 60 mL/minute/1.73 m². **Child 1 month–18 years** use normal dose every 8 hours if estimated glomerular filtration rate 30–60 mL/minute/1.73 m²; use half normal dose every 8 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; use half normal dose every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk, but appropriate to use

Side-effects see under Benzylpenicillin (section 5.1.1.1); also nausea, vomiting, coagulation disorders, haemorrhagic cystitis (more frequent in children), injection-site reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypokalaemia, eosinophilia

Indications and dose

Expressed as a combination of ticarcillin (as sodium salt) and clavulanic acid (as potassium salt) in a ratio of 15:1

Infections due to *Pseudomonas* and *Proteus* spp. see notes above

• By intravenous infusion

Preterm neonate body-weight under 2 kg 80 mg/kg every 12 hours

Preterm neonate body-weight over 2 kg and neonate 80 mg/kg every 8 hours, increased to every 6 hours in more severe infections

Child 1 month–18 years and body-weight under 40 kg 80 mg/kg every 8 hours, increased to every 6 hours in more severe infections

Child under 18 years and body-weight over 40 kg 3.2 g every 6–8 hours, increased to every 4 hours in more severe infections

Administration Displacement value may be important, consult local guidelines. For intermittent infusion, dilute reconstituted solution further to a concentration of 16–32 mg/mL with glucose 5%; infuse over 30–40 minutes.

Timentin® (GSK) (PoM)

Injection 3.2 g, powder for reconstitution, ticarcillin 3 g (as sodium salt), clavulanic acid 200 mg (as potassium salt). Net price per vial = £5.33

Electrolytes Na⁺ 16 mmol, K⁺ 1 mmol / 3.2-g vial

5.1.1.5 Mecillinams

Pivmecillinam has significant activity against many Gram-negative bacteria including *Escherichia coli*, klebsiella, enterobacter, and salmonellae. It is not active

against *Pseudomonas aeruginosa* or enterococci. Pivmecillinam is hydrolysed to mecillinam, which is the active drug.

PIVMECILLINAM HYDROCHLORIDE

Cautions see under Benzylpenicillin (section 5.1.1.1); also liver and renal function tests required in long-term use; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (penicillins)

Contra-indications see under Benzylpenicillin (section 5.1.1.1); also carnitine deficiency, oesophageal strictures, gastro-intestinal obstruction, infants under 3 months

Pregnancy not known to be harmful, but manufacturer advises avoid

Breast-feeding trace amounts in milk, but appropriate to use

Side-effects see under Benzylpenicillin (section 5.1.1.1); nausea, vomiting, abdominal pain, headache, dizziness; also reported mouth ulcers, oesophagitis, reduced serum and total body carnitine (especially with long-term or repeated use)

Licensed use not licensed for use in children under 3 months

Indications and dose

Acute uncomplicated cystitis

• By mouth

Child body-weight over 40 kg initially 400 mg then 200 mg every 8 hours for 3 days

Chronic or recurrent bacteriuria

Child body-weight over 40 kg 400 mg every 6–8 hours

Urinary-tract infections

Child body-weight under 40 kg 5–10 mg/kg every 6 hours; total daily dose may alternatively be given in 3 divided doses

Salmonellosis not recommended therefore no dose stated

Counselling Tablets should be swallowed whole with plenty of fluid during meals while sitting or standing

Selectid® (LEO) (PoM)

Tablets, f/c, pivmecillinam hydrochloride 200 mg, net price 10-tab pack = £4.50. Label: 9, 21, 27, counselling, posture (see Dose above)

5.1.2 Cephalosporins, carbapenems, and other beta-lactams

5.1.2.1 Cephalosporins

5.1.2.2 Carbapenems

5.1.2.3 Other beta-lactam antibiotics

Antibiotics in this section include the **cephalosporins**, such as cefotaxime, ceftazidime, cefuroxime, cefalexin and cefradine, the **monobactams**, aztreonam, and the **carbapenems**, imipenem (a thienamycin derivative), meropenem, and ertapenem.

5.1.2.1 Cephalosporins

The cephalosporins are broad-spectrum antibacterials which are used for the treatment of septicaemia, pneu-

monia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections. The pharmacology of the cephalosporins is similar to that of the penicillins, excretion being principally renal. Cephalosporins penetrate the cerebrospinal fluid poorly unless the meninges are inflamed; cefotaxime and ceftriaxone are suitable cephalosporins for infections of the CNS (e.g. meningitis).

The principal side-effect of the cephalosporins is hypersensitivity and about 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. Patients with a history of immediate hypersensitivity to penicillin should not receive a cephalosporin. If a cephalosporin is essential in these patients because a suitable alternative antibacterial is not available, then cefixime, cefotaxime, ceftazidime, ceftriaxone, or cefuroxime can be used with caution; cefaclor, cefadroxil, cefalexin, and cefradine should be avoided.

Antibiotic-associated colitis may occur with the use of broad-spectrum cephalosporins, particularly second- and third-generation cephalosporins.

Cefuroxime is a 'second generation' cephalosporin that is less susceptible than the earlier cephalosporins to inactivation by beta-lactamases. It is, therefore, active against certain bacteria that are resistant to the other drugs and has greater activity against *Haemophilus influenzae*.

Cefotaxime, ceftazidime and ceftriaxone are 'third generation' cephalosporins with greater activity than the 'second generation' cephalosporins against certain Gram-negative bacteria. However, they are less active than cefuroxime against Gram-positive bacteria, most notably *Staphylococcus aureus*. Their broad antibacterial spectrum may encourage superinfection with resistant bacteria or fungi.

Ceftazidime has good activity against pseudomonas. It is also active against other Gram-negative bacteria.

Ceftriaxone has a longer half-life and therefore needs to be given only once daily. Indications include serious infections such as septicaemia, pneumonia, and meningitis. The calcium salt of ceftriaxone forms a precipitate in the gall bladder which may rarely cause symptoms but these usually resolve when the antibacterial is stopped. In neonates, ceftriaxone may displace bilirubin from plasma-albumin and should be avoided in neonates with unconjugated hyperbilirubinaemia, hypocalcaemia, acidosis or impaired bilirubin binding.

Orally active cephalosporins The orally active 'first generation' cephalosporins, **cefalexin, cefradine, and cefadroxil** and the 'second generation' cephalosporin, **cefaclor**, have a similar antimicrobial spectrum. They are useful for urinary-tract infections which do not respond to other drugs or which occur in pregnancy, respiratory-tract infections, otitis media, sinusitis, and skin and soft-tissue infections. Cefaclor has good activity against *H. influenzae*, but it is associated with protracted skin reactions especially in children. Cefadroxil has a long duration of action and can be given twice daily; it has poor activity against *H. influenzae*. **Cefuroxime axetil**, an ester of the 'second generation' cephalosporin cefuroxime, has the same antibacterial spectrum as the parent compound; it is poorly absorbed and needs to be given with food to maximise absorption.

Cefixime is an orally active 'third generation' cephalosporin. It has a longer duration of action than the other

cephalosporins that are active by mouth. It is only licensed for acute infections.

For treatment of Lyme disease, see section 5.1.1.3.

Oral infections The cephalosporins offer little advantage over the penicillins in dental infections, often being less active against anaerobes. Infections due to oral streptococci (often termed viridans streptococci) which become resistant to penicillin are usually also resistant to cephalosporins. This is of importance in the case of children who have had rheumatic fever and are on long-term penicillin therapy. Cefalexin and cefradine have been used in the treatment of oral infections.

CEFACLOR

Cautions sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also notes above and p. 261); false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; **interactions:** Appendix 1 (cephalosporins)

Contra-indications cephalosporin hypersensitivity

Renal impairment no dosage adjustment required, manufacturer advises caution

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration, but appropriate to use

Side-effects diarrhoea (rarely antibiotic-associated colitis), nausea and vomiting, abdominal discomfort, headache; allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions with rashes, fever and arthralgia, and anaphylaxis; Stevens-Johnson syndrome, toxic epidermal necrolysis reported; disturbances in liver enzymes, transient hepatitis and cholestatic jaundice; other side-effects reported include eosinophilia and blood disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hypertonia, and dizziness

Indications and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above

• By mouth

Child 1 month–12 years 20 mg/kg daily in 3 divided doses, doubled for severe infection (usual max. 1 g daily)

or

Child 1 month–1 year 62.5 mg 3 times daily; dose doubled for severe infections

Child 1–5 years 125 mg 3 times daily; dose doubled for severe infections

Child 5–12 years 250 mg 3 times daily; dose doubled for severe infections

Child 12–18 years 250 mg 3 times daily; dose doubled for severe infections (max. 4 g daily)

Asymptomatic carriage of *Haemophilus influenzae* or mild exacerbations in cystic fibrosis

• By mouth

Child 1 month–1 year 125 mg every 8 hours

Child 1–7 years 250 mg 3 times daily

Child 7–18 years 500 mg 3 times daily

Cefaclor (Non-proprietary) (PoM)

Capsules, cefaclor (as monohydrate) 250 mg, net price 21-cap pack = £6.80; 500 mg, 50-cap pack = £24.00. Label: 9

Brands include *Keftid*[®]

Suspension, cefaclor (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £5.16; 250 mg/5 mL, 100 mL = £10.32. Label: 9

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Brands include *Keftid*[®]

Distaclor[®] (Flynn) (PoM)

Capsules, cefaclor (as monohydrate) 500 mg (violet/grey), net price 21-cap pack = £7.50. Label: 9

Suspension, both pink, cefaclor (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £4.13; 250 mg/5 mL, 100 mL = £8.26. Label: 9

Distaclor MR[®] (Flynn) (PoM)

Tablets, m/r, both blue, cefaclor (as monohydrate) 375 mg. Net price 14-tab pack = £9.10. Label: 9, 21, 25

Dose

Susceptible infections

Child 12–18 years 375 mg every 12 hours with food, dose doubled for pneumonia

Lower urinary-tract infections

Child 12–18 years 375 mg every 12 hours with food

CEFADROXIL

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment reduce dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration, but appropriate to use

Side-effects see under Cefaclor

Indications and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above

- By mouth

Child 6–18 years

Body-weight under 40 kg 500 mg twice daily;

Body-weight over 40 kg 0.5–1 g twice daily (1 g once daily for skin, soft-tissue and uncomplicated urinary-tract infections)

Cefadroxil (Non-proprietary) (PoM)

Capsules, cefadroxil (as monohydrate) 500 mg, net price 20-cap pack = £20.89. Label: 9

CEFALEXIN

(Cephalexin)

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment reduce dose in moderate impairment

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration, but appropriate to use

Side-effects see under Cefaclor

Indications and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above

- By mouth

Neonate under 7 days 25 mg/kg (max. 125 mg) twice daily

Neonate 7–21 days 25 mg/kg (max. 125 mg) 3 times daily

Neonate 21–28 days 25 mg/kg (max. 125 mg) 4 times daily

Child 1 month–12 years 12.5 mg/kg twice daily; dose doubled in severe infection; max. 25 mg/kg 4 times daily (max. 1 g 4 times daily)

or

Child 1 month–1 year 125 mg twice daily

Child 1–5 years 125 mg 3 times daily

Child 5–12 years 250 mg 3 times daily

Child 12–18 years 500 mg 2–3 times daily, increased to 1–1.5 g 3–4 times daily for severe infection

Prophylaxis of recurrent urinary-tract infection

- By mouth

Child 1 month–18 years 12.5 mg/kg at night (max. 125 mg at night)

Cefalexin (Non-proprietary) (PoM)

Capsules, cefalexin 250 mg, net price 28-cap pack = £1.67; 500 mg, 21-cap pack = £1.77. Label: 9

Dental prescribing on NHS Cefalexin Capsules may be prescribed

Tablets, cefalexin 250 mg, net price 28-tab pack = £2.02; 500 mg, 21-tab pack = £2.53. Label: 9

Dental prescribing on NHS Cefalexin Tablets may be prescribed

Oral suspension, cefalexin for reconstitution with water, 125 mg/5 mL, net price 100 mL = £1.40; 250 mg/5 mL, 100 mL = £1.89. Label: 9

Dental prescribing on NHS Cefalexin Oral Suspension may be prescribed

Ceporex[®] (Co-Pharma) (PoM)

Capsules, both caramel/grey, cefalexin 250 mg, net price 28-cap pack = £4.02; 500 mg, 28-cap pack = £7.85. Label: 9

Tablets, all pink, f/c, cefalexin 250 mg, net price 28-tab pack = £4.02; 500 mg, 28-tab pack = £7.85. Label: 9

Syrup, all orange, cefalexin for reconstitution with water, 125 mg/5 mL, net price 100 mL = £1.43; 250 mg/5 mL, 100 mL = £2.87; 500 mg/5 mL, 100 mL = £5.57. Label: 9

Keflex[®] (Flynn) (PoM)

Capsules, cefalexin 250 mg (green/white), net price 28-cap pack = £1.46; 500 mg (pale green/dark green), 21-cap pack = £1.98. Label: 9

Tablets, both peach, cefalexin 250 mg, net price 28-tab pack = £1.60; 500 mg (scored), 21-tab pack = £2.08. Label: 9

Suspension, cefalexin for reconstitution with water, 125 mg/5 mL, net price 100 mL = 84p; 250 mg/5 mL, 100 mL = £1.40. Label: 9

CEFIXIME

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment reduce dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Pregnancy not known to be harmful

Breast-feeding manufacturer advises avoid unless essential—no information available

Side-effects see under Cefaclor

Indications and dose

Acute infections due to sensitive Gram-positive and Gram-negative bacteria, but see notes above

- By mouth

Child 6 months–1 year 75 mg daily

Child 1–5 years 100 mg daily

Child 5–10 years 200 mg daily

Child 10–18 years 200–400 mg daily or 100–200 mg twice daily

Uncomplicated gonorrhoea [unlicensed indication, see also Table 1, section 5.1]

- By mouth

Child 12–18 years 400 mg as a single dose

Suprax® (Sanofi-Aventis) (PoM)

Tablets, f/c, scored, cefixime 200 mg. Net price 7-tab pack = £13.23. Label: 9

Paediatric oral suspension, cefixime 100 mg/5 mL when reconstituted with water, net price 100 mL (with spoon for measuring 3.75 mL or 5 mL) = £18.91. Label: 9

CEFOTAXIME

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment usual initial dose, then use half normal dose if estimated glomerular filtration rate less than 5 mL/minute/1.73 m²

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration, but appropriate to use

Side-effects see under Cefaclor; rarely arrhythmias following rapid injection reported

Indications and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria, surgical prophylaxis, *Haemophilus epiglottitis* and meningitis (Table 1, section 5.1) see also notes above

- By intramuscular or by intravenous injection or intravenous infusion

Neonate under 7 days 25 mg/kg every 12 hours; dose doubled in severe infection and meningitis

Neonate 7–21 days 25 mg/kg every 8 hours; dose doubled in severe infection and meningitis

Neonate 21–28 days 25 mg/kg every 6–8 hours; dose doubled in severe infection and meningitis

Child 1 month–18 years 50 mg/kg every 8–12 hours; increase to every 6 hours in very severe infections and meningitis (max. 12 g daily)

Important. If meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) is

suspected, and the child cannot be given benzylpenicillin (e.g. because of an allergy), a single dose of cefotaxime can be given (if available) before urgent transfer to hospital, so long as this does not delay the transfer. If a child with suspected bacterial meningitis without non-blanching rash cannot be transferred to hospital urgently and cannot be given benzylpenicillin, a single dose of cefotaxime can be given before transfer. Suitable doses of cefotaxime by intravenous injection (or by intramuscular injection) are **Child under 12 years** 50 mg/kg; **Child over 12 years** 1 g; chloramphenicol (section 5.1.7) may be used if there is a history of anaphylaxis to penicillins or cephalosporins

Congenital gonococcal conjunctivitis

- By intramuscular injection

Neonate 100 mg/kg (max. 1 g) as a single dose

Uncomplicated gonorrhoea

- By intramuscular injection

Child 12–18 years 500 mg as a single dose

Severe exacerbations of *Haemophilus influenzae* infection in cystic fibrosis

- By intravenous injection or intravenous infusion

Child 1 month–18 years 50 mg/kg every 6–8 hours (max. 12 g daily)

Administration Displacement value may be significant, consult local guidelines. For intermittent intravenous infusion dilute in glucose 5% or sodium chloride 0.9%; administer over 20–60 minutes; incompatible with alkaline solutions

Cefotaxime (Non-proprietary) (PoM)

Injection, powder for reconstitution, cefotaxime (as sodium salt), net price 500-mg vial = £2.25; 1-g vial = £4.20; 2-g vial = £8.57

CEFRADINE
(Cephadrine)

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment reduce dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration, but appropriate to use

Side-effects see under Cefaclor

Licensed use not licensed for use in children for prevention of *Staphylococcus aureus* lung infection in cystic fibrosis

Indications and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above

- By mouth

Child 7–12 years 12.5–25 mg/kg twice daily (total daily dose may alternatively be given in 3–4 divided doses)

Child 12–18 years 0.5–1 g twice daily or 250–500 mg 4 times daily; up to 1 g 4 times daily in severe infections

Prevention of *Staphylococcus aureus* lung infection in cystic fibrosis

- By mouth

Child 7–18 years 2 g twice daily

Cefradine (Non-proprietary) (PoM)

Capsules, cefradine 250 mg, net price 20-cap pack = £2.34; 500 mg, 20-cap pack = £3.47. Label: 9

Brands include *Nicef*®

Dental prescribing on NHS Cefradine Capsules may be prescribed

CEFTAZIDIME

Cautions see under Cefaclor; **interactions**: Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Hepatic impairment manufacturer advises caution in severe impairment

Renal impairment reduce dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²—consult product literature

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration, but appropriate to use

Side-effects see under Cefaclor; also taste disturbances, paraesthesia

Licensed use nebulised route unlicensed

Indications and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above

- By intravenous injection or infusion

Neonate under 7 days 25 mg/kg every 24 hours; dose doubled in severe infection and meningitis

Neonate 7–21 days 25 mg/kg every 12 hours; dose doubled in severe infection and meningitis

Neonate 21–28 days 25 mg/kg every 8 hours; dose doubled in severe infection and meningitis

Child 1 month–18 years 25 mg/kg every 8 hours; dose doubled in severe infection, febrile neutropenia and meningitis (max. 6 g daily)

Pseudomonal lung infection in cystic fibrosis

- By intravenous injection or infusion (or by deep intramuscular injection if intravenous administration not possible)

Child 1 month–18 years 50 mg/kg every 8 hours (max. 9 g daily); single doses over 1 g intravenous route only

Chronic *Burkholderia cepacia* infection in cystic fibrosis

- By inhalation of nebulised solution

Child 1 month–18 years 1 g twice daily

Administration For parenteral administration, intravenous route recommended in children. Displacement value may be significant, consult local guidelines. For intermittent intravenous infusion dilute reconstituted solution further to a concentration of not more than 40 mg/mL in Glucose 5% or Glucose 10% or Sodium chloride 0.9%; give over 20–30 minutes

For nebulisation, dissolve dose in 3 mL of water for injection

Ceftazidime (Non-proprietary) (PoM)

Injection, powder for reconstitution, ceftazidime (as pentahydrate), with sodium carbonate, net price 1-g vial = £8.95; 2-g vial = £17.90

Fortum® (GSK) (PoM)

Injection, powder for reconstitution, ceftazidime (as pentahydrate), with sodium carbonate, net price 500-mg vial = £4.40, 1-g vial = £8.79, 2-g vial = £17.59, 3-g vial = £25.76

Electrolytes Na⁺ 2.3 mmol/g

Kefadim® (Flynn) (PoM)

Injection, powder for reconstitution, ceftazidime (as pentahydrate), with sodium carbonate, net price 1-g vial = £7.92; 2-g vial = £15.84

Electrolytes Na⁺ 2.3 mmol/g

CEFTRIAXONE

Cautions see under Cefaclor; neonates; may displace bilirubin from serum albumin, administer over 60 minutes in neonates (see also Contra-indications); treatment longer than 14 days, renal failure, dehydration—risk of ceftriaxone precipitation in gall bladder; **interactions**: Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor; neonates less than 41 weeks corrected gestational age; neonates over 41 weeks corrected gestational age with jaundice, hypoalbuminaemia, or acidosis; concomitant treatment with intravenous calcium (including total parenteral nutrition containing calcium) in neonates over 41 weeks corrected gestational age—risk of precipitation in urine and lungs

Hepatic impairment if hepatic impairment is accompanied by severe renal impairment, reduce dose and monitor plasma concentration

Renal impairment max. 50 mg/kg daily (max. 2 g daily) in severe renal impairment; also monitor plasma concentration if hepatic impairment accompanied by severe renal impairment

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration, but appropriate to use

Side-effects see under Cefaclor; calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated or those who are immobilised) or in gall bladder—consider discontinuation if symptomatic; rarely prolongation of prothrombin time, pancreatitis

Licensed use not licensed for congenital gonococcal conjunctivitis or early syphilis; not licensed for prophylaxis of meningococcal meningitis or *Haemophilus influenzae* type b disease; not licensed for use in children under 12 years of age for uncomplicated gonorrhoea or pelvic inflammatory disease

Indications and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria

- By intravenous infusion over 60 minutes

Neonate 20–50 mg/kg once daily

- By deep intramuscular injection, or by intravenous injection over 2–4 minutes, or by intravenous infusion

Child 1 month–12 years

Body-weight under 50 kg 50 mg/kg once daily; up to 80 mg/kg daily in severe infections and

meningitis; doses of 50 mg/kg and over by intravenous infusion only

Body-weight 50 kg and over dose as for child 12–18 years

Child 12–18 years 1 g daily; 2–4 g daily in severe infections and meningitis; intramuscular doses over 1 g divided between more than one site; single intravenous doses above 1 g by intravenous infusion only

Congenital gonococcal conjunctivitis

- By intravenous infusion over 60 minutes or by deep intramuscular injection

Neonate 25–50 mg/kg (max. 125 mg) as a single dose

Uncomplicated gonorrhoea, pelvic inflammatory disease (Table 1, section 5.1)

- By deep intramuscular injection

Child under 12 years

Body-weight under 45 kg 125 mg as a single dose

Body-weight over 45 kg 250 mg as a single dose

Child 12–18 years 250 mg as a single dose

Early syphilis

- By deep intramuscular injection

Child 12–18 years 500 mg daily for 10 days

Surgical prophylaxis

- By deep intramuscular injection or by intravenous injection over at least 2–4 minutes, or (for colorectal surgery) by intravenous infusion

Child 12–18 years 1 g up to 30 minutes before the procedure; colorectal surgery, 2 g up to 30 minutes before the procedure; intramuscular doses over 1 g divided between more than one site

Prophylaxis of meningococcal meningitis Table 2, section 5.1

Prophylaxis of *Haemophilus influenzae* type b disease Table 2, section 5.1

Administration Displacement value may be significant, consult local guidelines. For *intravenous infusion*, dilute reconstituted solution with Glucose 5% or 10% or Sodium Chloride 0.9%; give over at least 30 minutes (60 minutes in neonates). Not to be given simultaneously with parenteral nutrition or infusion fluids containing calcium, even by different infusion lines; may be infused sequentially with infusion fluids containing calcium if flush with sodium chloride 0.9% between infusions or give infusions by different infusion lines at different sites; see also Contra-indications above

For *intramuscular injection* ceftriaxone may be mixed with 1% Lidocaine Hydrochloride Injection to reduce pain at intramuscular injection site; final concentration 250–350 mg/mL.

Ceftriaxone (Non-proprietary) (PoM)

Injection, powder for reconstitution, ceftriaxone (as sodium salt), net price 1-g vial = £9.58; 2-g vial = £19.18

Rocephin® (Roche) (PoM)

Injection, powder for reconstitution, ceftriaxone (as sodium salt), net price 250-mg vial = £2.40; 1-g vial = £9.58; 2-g vial = £19.18

Electrolytes Na⁺ 3.6 mmol/g

CEFUROXIME

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment reduce parenteral dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration, but appropriate to use

Side-effects see under Cefaclor

Licensed use not licensed for treatment of Lyme disease in children under 12 years

Indications and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria

- By mouth (as cefuroxime axetil)

Child 3 months–2 years 10 mg/kg (max. 125 mg) twice daily

Child 2–12 years 15 mg/kg (max. 250 mg) twice daily

Child 12–18 years 250 mg twice daily; dose doubled in severe lower respiratory-tract infections, or if pneumonia suspected; dose reduced to 125 mg twice daily in lower urinary-tract infection

- By intravenous injection or infusion or by intramuscular injection

Neonate under 7 days 25 mg/kg every 12 hours; dose doubled in severe infection, intravenous route only

Neonate 7–21 days 25 mg/kg every 8 hours; dose doubled in severe infection, intravenous route only

Neonate 21–28 days 25 mg/kg every 6 hours; dose doubled in severe infection, intravenous route only

Child 1 month–18 years 20 mg/kg (max. 750 mg) every 8 hours; increase to 50–60 mg/kg (max. 1.5 g) every 6–8 hours in severe infection and cystic fibrosis

Lyme disease (see also section 5.1.1.3)

- By mouth

Child 3 months–12 years 15 mg/kg (max. 500 mg) twice daily for 14–21 days (for 28 days in Lyme arthritis)

Child 12–18 years 500 mg twice daily for 14–21 days (for 28 days in Lyme arthritis)

Surgical prophylaxis

- By intravenous injection

Child 1 month–18 years 50 mg/kg (max. 1.5 g) up to 30 minutes before the procedure; up to 3 further doses of 30 mg/kg (max. 750 mg) may be given by *intramuscular or intravenous injection* every 8 hours for high-risk procedures

Administration Single doses over 750 mg should be administered by the intravenous route only.

Displacement value may be significant when reconstituting injection, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9%; give over 30 minutes.

Cefuroxime (Non-proprietary) (PoM)

Tablets, cefuroxime (as axetil) 250 mg, net price 14-tab pack = £14.67. Label: 9, 21, 25

Injection, powder for reconstitution, cefuroxime (as sodium salt), net price 750-mg vial = £2.52; 1.5-g vial = £5.05

Zinacef[®] (GSK) (PoM)

Injection, powder for reconstitution, cefuroxime (as sodium salt). Net price 250-mg vial = 94p; 750-mg vial = £2.34; 1.5-g vial = £4.70

Electrolytes Na⁺ 1.8 mmol/750-mg vial

Zinnat[®] (GSK) (PoM)

Tablets, both f/c, cefuroxime (as axetil) 125 mg, net price 14-tab pack = £4.56; 250 mg, 14-tab pack = £9.11. Label: 9, 21, 25

Suspension, cefuroxime (as axetil) 125 mg/5 mL when reconstituted with water, net price 70 mL (tutti-frutti-flavoured) = £5.20. Label: 9, 21

Excipients include aspartame (section 9.4.1), sucrose 3.1 g/5 mL

5.1.2.2 Carbapenems

The carbapenems are beta-lactam antibacterials with a broad-spectrum of activity which includes many Gram-positive and Gram-negative bacteria, and anaerobes; **imipenem** and **meropenem** have good activity against *Pseudomonas aeruginosa*. The carbapenems are not active against methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecium*.

Imipenem and meropenem are used for the treatment of severe hospital-acquired infections and polymicrobial infections caused by multiple-antibacterial resistant organisms (including septicaemia, hospital-acquired pneumonia, intra-abdominal infections, skin and soft-tissue infections, and complicated urinary-tract infections).

Ertapenem is licensed for treating abdominal and gynaecological infections and for community-acquired pneumonia, but it is not active against atypical respiratory pathogens and it has limited activity against penicillin-resistant pneumococci. Unlike the other carbapenems, ertapenem is not active against *Pseudomonas* or against *Acinetobacter* spp.

Imipenem is partially inactivated in the kidney by enzymatic activity and is therefore administered in combination with **cilastatin**, a specific enzyme inhibitor, which blocks its renal metabolism. Meropenem and ertapenem are stable to the renal enzyme which inactivates imipenem and therefore can be given without cilastatin.

Side-effects of imipenem with cilastatin are similar to those of other beta-lactam antibiotics; neurotoxicity has been observed at very high dosage, in renal failure, or in patients with CNS disease. Meropenem has less seizure-inducing potential and can be used to treat central nervous system infection. Ertapenem has been associated with seizures uncommonly.

ERTAPENEM

Cautions hypersensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 261); renal impairment, CNS disorders—risk of seizures; **interactions**: Appendix 1 (ertapenem)

Renal impairment risk of seizures; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk

Breast-feeding present in milk—manufacturer advises avoid

Side-effects diarrhoea, nausea, vomiting, headache, injection-site reactions, rash (also reported with eosinophilia and systemic symptoms), pruritus, raised platelet count; *less commonly* dry mouth, taste disturbances, dyspepsia, abdominal pain, anorexia, constipation, melaena, antibiotic-associated colitis, bradycardia, hypotension, chest pain, oedema, pharyngeal discomfort, dyspnoea, dizziness, sleep disturbances, confusion, asthenia, seizures, raised glucose, petechiae; *rarely* dysphagia, cholecystitis, liver disorder (including jaundice), arrhythmia, increase in blood pressure, syncope, nasal congestion, cough, wheezing, anxiety, depression, agitation, tremor, pelvic peritonitis, renal impairment, muscle cramp, scleral disorder, blood disorders (including neutropenia, thrombocytopenia, haemorrhage), hypoglycaemia, electrolyte disturbances; also reported hallucinations, dyskinesia, muscular weakness

Indications and dose

Abdominal infections, acute gynaecological infections, community-acquired pneumonia

- By intravenous infusion

Child 3 months–13 years 15 mg/kg every 12 hours (max. 1 g daily)

Child 13–18 years 1 g once daily

Administration reconstitute 1 g with 10 mL Water for Injections or Sodium Chloride 0.9%; for *intravenous infusion*, dilute requisite dose in Sodium Chloride 0.9% to a final concentration not exceeding 20 mg/mL; give over 30 minutes; incompatible with glucose solutions

Invanz[®] (MSD) (PoM)

Intravenous infusion, powder for reconstitution, ertapenem (as sodium salt), net price 1-g vial = £31.65

Electrolytes Na⁺ 6 mmol/1-g vial

IMIPENEM WITH CILASTATIN

Cautions CNS disorders (e.g. epilepsy); hypersensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 261); **interactions**: Appendix 1 (imipenem with cilastatin)

Renal impairment reduce dose if estimated glomerular filtration rate less than 70 mL/minute/1.73 m²; risk of CNS side-effects

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk (toxicity in *animal* studies)

Breast-feeding present in milk but unlikely to be absorbed

Side-effects nausea (may reduce rate of infusion), vomiting, diarrhoea (rarely antibiotic-associated colitis), eosinophilia, rash (rarely toxic epidermal necrolysis and Stevens-Johnson syndrome); *less commonly* hypotension, seizures, myoclonic activity, dizziness, drowsiness, hallucinations, confusion, leucopenia, thrombocytopenia, thrombocytosis, positive Coombs' test; *rarely* taste disturbances, hepatitis, encephalopathy, anaphylactic reactions, paraesthesia, tremor, acute renal failure, polyuria, tooth, tongue or urine

discoloration, hearing loss; *very rarely*, abdominal pain, heartburn, glossitis, tachycardia, palpitation, flushing, cyanosis, dyspnoea, hyperventilation, headache, asthma, haemolytic anaemia, aggravation of myasthenia gravis, polyarthralgia, tinnitus, hypersalivation, hyperhidrosis

Licensed use not licensed for use in children under 1 year; not licensed for use in children with renal impairment

Indications and dose

Aerobic and anaerobic Gram-positive and Gram-negative infections, hospital-acquired septicæmia Table 1, section 5.1; not indicated for CNS infections

- **By intravenous infusion**

expressed in terms of imipenem

Neonate under 7 days 20 mg/kg every 12 hours

Neonate 7–21 days 20 mg/kg every 8 hours

Neonate 21–28 days 20 mg/kg every 6 hours

Child 1–3 months 20 mg/kg every 6 hours

Child 3 months–18 years 15 mg/kg (max. 500 mg) every 6 hours; infection caused by *Pseudomonas* or other less sensitive organisms, life-threatening infection, or empirical treatment of infection in febrile patients with neutropenia, 25 mg/kg (max. 1 g) every 6 hours

Cystic fibrosis

- **By intravenous infusion**

Child 1 month–18 years 25 mg/kg (max. 1 g) every 6 hours

Administration for *intravenous infusion* dilute to a concentration of 5 mg (as imipenem)/mL in Sodium Chloride 0.9%; give up to 500 mg (as imipenem) over 20–30 minutes, give dose greater than 500 mg (as imipenem) over 40–60 minutes

Imipenem with cilastatin (Non-proprietary) (PoM)

Intravenous infusion, powder for reconstitution, imipenem (as monohydrate) 500 mg with cilastatin (as sodium salt) 500 mg, net price per vial = £12.00

Primaxin® (MSD) (PoM)

Intravenous infusion, powder for reconstitution, imipenem (as monohydrate) 500 mg with cilastatin (as sodium salt) 500 mg, net price per vial = £12.00

Electrolytes Na⁺ 1.6 mmol/vial

MEROPEM

Cautions hypersensitivity to beta-lactam antibiotics (avoid if history of immediate hypersensitivity reaction, see also p. 261); **interactions:** Appendix 1 (meropenem)

Hepatic impairment monitor liver function

Renal impairment use normal dose every 12 hours if estimated glomerular filtration rate 26–50 mL/minute/1.73 m²; use half normal dose every 12 hours if estimated glomerular filtration rate 10–25 mL/minute/1.73 m²; use half normal dose every 24 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy use only if potential benefit outweighs risk—no information available

Breast-feeding unlikely to be absorbed (but manufacturer advises avoid)

Side-effects nausea, vomiting, diarrhoea (antibiotic-associated colitis reported), abdominal pain, disturbances in liver function tests, headache, thrombocythaemia, rash, pruritus; *less commonly* paraesthesia, eosinophilia, thrombocytopenia, leucopenia; *rarely* convulsions; also reported haemolytic anaemia, positive Coombs' test, Stevens-Johnson syndrome, toxic epidermal necrolysis

Licensed use not licensed for use in children under 3 months

Indications and dose

Aerobic and anaerobic Gram-positive and Gram-negative infections (see notes above), hospital-acquired septicæmia Table 1, section 5.1

- **By intravenous injection over 5 minutes or by intravenous infusion**

Neonate under 7 days 20 mg/kg every 12 hours, dose doubled in severe infection

Neonate 7–28 days 20 mg/kg every 8 hours; dose doubled in severe infection

Child 1 month–12 years

Body-weight under 50 kg 10–20 mg/kg every 8 hours

Body-weight over 50 kg dose as for child 12–18 years

Child 12–18 years 0.5–1 g every 8 hours

Meningitis

- **By intravenous infusion**

Neonate under 7 days 40 mg/kg every 12 hours

Neonate 7–28 days 40 mg/kg every 8 hours

Child 1 month–12 years

Body-weight under 50 kg 40 mg/kg every 8 hours

Body-weight over 50 kg dose as for child 12–18 years

Child 12–18 years 2 g every 8 hours

Exacerbations of chronic lower respiratory-tract infections in cystic fibrosis

- **By intravenous infusion**

Child 1 month–12 years

Body-weight under 50 kg 40 mg/kg every 8 hours

Body-weight over 50 kg dose as for child 12–18 years

Child 12–18 years 2 g every 8 hours

Administration displacement value may be significant when reconstituting injection, consult local guidelines. For *intravenous infusion*, dilute reconstituted solution further to a concentration of 1–20 mg/mL in Glucose 5% or Sodium Chloride 0.9%; give over 15–30 minutes

Meropenem (Non-proprietary) (PoM)

Injection, powder for reconstitution, meropenem (as trihydrate), net price 500-mg vial = £8.00; 1-g vial = £16.00

Meronom® (AstraZeneca) (PoM)

Injection, powder for reconstitution, meropenem (as trihydrate), net price 500-mg vial = £10.31; 1-g vial = £20.63

Electrolytes Na⁺ 3.9 mmol/g

5.1.2.3 Other beta-lactam antibiotics

Aztreonam is a monocyclic beta-lactam ('monobactam') antibiotic with an antibacterial spectrum limited to Gram-negative aerobic bacteria including *Pseudomonas aeruginosa*, *Neisseria meningitidis*, and *Haemophilus influenzae*; it should not be used alone for 'blind' treatment since it is not active against Gram-positive organisms. Aztreonam is also effective against *Neisseria gonorrhoeae* (but not against concurrent chlamydial infection). Side-effects are similar to those of the other beta-lactams although aztreonam may be less likely to cause hypersensitivity in penicillin-sensitive patients.

Aztreonam may be administered by nebuliser for the treatment of chronic *Ps. aeruginosa* infection in cystic fibrosis.

AZTREONAM

Cautions hypersensitivity to beta-lactam antibiotics; **interactions:** Appendix 1 (aztreonam)

Specific cautions for inhaled treatment Other inhaled drugs should be administered before aztreonam; a bronchodilator should be administered before each dose. Measure lung function before and after initial dose of aztreonam and monitor for bronchospasm. Haemoptysis—risk of further haemorrhage

Contra-indications aztreonam hypersensitivity

Hepatic impairment use injection with caution and monitor liver function

Renal impairment if estimated glomerular filtration rate 10–30 mL/minute/1.73 m², usual initial dose of injection, then half normal dose; if estimated glomerular filtration rate less than 10 mL/minute/1.73 m², usual initial dose of injection, then one-quarter normal dose

Pregnancy no information available; manufacturer of injection advises avoid; manufacturer of powder for nebuliser solution advises avoid unless essential

Breast-feeding amount in milk probably too small to be harmful

Side-effects

Specific side-effects for parenteral treatment Rarely gastro-intestinal bleeding, antibiotic-associated colitis, jaundice, hepatitis, hypotension, chest pain, dyspnoea, seizures, paraesthesia, confusion, dizziness, asthenia, headache, insomnia, breast tenderness, blood disorders (including thrombocytopenia and neutropenia), myalgia, diplopia, tinnitus, halitosis; also reported nausea, vomiting, abdominal pain, diarrhoea, mouth ulcers, taste disturbances, flushing, bronchospasm, rash (including toxic epidermal necrolysis and erythema multiforme)

Specific side-effects for inhaled treatment Wheezing, bronchospasm, cough, haemoptysis, pyrexia, arthralgia, rash, rhinorrhoea, pharyngolaryngeal pain

Licensed use injection not licensed for use in children under 7 days

Indications and dose

Gram-negative infections including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis*

- By intravenous injection over 3–5 minutes or by intravenous infusion

Neonate under 7 days 30 mg/kg every 12 hours

Neonate 7–28 days 30 mg/kg every 6–8 hours

Child 1 month–2 years 30 mg/kg every 6–8 hours

Child 2–12 years 30 mg/kg every 6–8 hours increased to 50 mg/kg every 6–8 hours in severe infection and cystic fibrosis (max. 2 g every 6 hours)

Child 12–18 years 1 g every 8 hours or 2 g every 12 hours; 2 g every 6–8 hours for severe infections (including systemic *Ps. aeruginosa* and lung infections in cystic fibrosis)

Chronic pulmonary *Pseudomonas aeruginosa* infection in patients with cystic fibrosis

- By inhalation of nebulised solution

Child 6–18 years 75 mg 3 times daily (at least 4 hours apart) for 28 days, subsequent courses repeated after 28-day interval without aztreonam nebuliser solution

Administration Displacement value of injection may be significant, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in Glucose 5% or Sodium chloride 0.9% to a concentration of less than 20 mg/mL; to be given over 20–60 minutes

Parenteral

Azactam® (Squibb) (PoM)

Injection, powder for reconstitution, aztreonam. Net price 1-g vial = £9.40; 2-g vial = £18.82

Inhalation

Cayston® (Gilead) (PoM)

Powder for nebuliser solution, aztreonam (as lysine), net price 84 × 75 mg vials (with solvent and nebuliser handset) = £2566.50

5.1.3 Tetracyclines

The tetracyclines are broad-spectrum antibiotics whose value has decreased owing to increasing bacterial resistance. In children over 12 years of age they are useful for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and lymphogranuloma venereum), rickettsia (including Q-fever), brucella (doxycycline with either streptomycin or rifampicin), and the spirochaete, *Borrelia burgdorferi* (Lyme disease—see section 5.1.1.3). They are also used in respiratory and genital mycoplasma infections, in acne, in destructive (refractory) periodontal disease, in exacerbations of chronic respiratory diseases (because of their activity against *Haemophilus influenzae*), and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin).

Microbiologically, there is little to choose between the various tetracyclines, the only exception being **minocycline** which has a broader spectrum; it is active against *Neisseria meningitidis* and has been used for meningococcal prophylaxis but is no longer recommended because of side-effects including dizziness and vertigo (see Table 2, section 5.1 for current recommendations). Compared to other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation.

For the role of tetracyclines in the management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections, see p. 263.

Oral infections In children over 12 years of age, tetracyclines can be effective against oral anaerobes but the development of resistance (especially by oral streptococci) has reduced their usefulness for the treatment of acute oral infections; they may still have a role in the treatment of destructive (refractory) forms of period-

ontal disease. Doxycycline has a longer duration of action than tetracycline or oxytetracycline and need only be given once daily; it is reported to be more active against anaerobes than some other tetracyclines.

For the use of doxycycline in the treatment of recurrent aphthous ulceration, or as an adjunct to gingival scaling and root planing for periodontitis, see section 12.3.1.

Cautions Tetracyclines may increase muscle weakness in patients with myasthenia gravis, and exacerbate systemic lupus erythematosus. Antacids, and aluminium, calcium, iron, magnesium and zinc salts decrease the absorption of tetracyclines; milk also reduces the absorption of demeclocycline, oxytetracycline, and tetracycline. Other **interactions**: Appendix 1 (tetracyclines).

Contra-indications Deposition of tetracyclines in growing bone and teeth (by binding to calcium) causes staining and occasionally dental hypoplasia, and they should **not** be given to children under 12 years, or to pregnant or breast-feeding women. However, doxycycline may be used in children for treatment and post-exposure prophylaxis of anthrax when an alternative antibacterial cannot be given [unlicensed indication].

Hepatic impairment Tetracyclines should be avoided or used with caution in children with hepatic impairment. Tetracyclines should also be used with caution in those receiving potentially hepatotoxic drugs.

Renal impairment With the exception of doxycycline and minocycline, the tetracyclines may exacerbate renal failure and should **not** be given to children with renal impairment.

Pregnancy Tetracyclines should **not** be given to pregnant women; effects on skeletal development have been documented in the first trimester in *animal* studies. Administration during the second or third trimester may cause discoloration of the child's teeth, and maternal hepatotoxicity has been reported with large parenteral doses. However, when travel to malarious areas is unavoidable during pregnancy, doxycycline can be used for malaria prophylaxis if other regimens are unsuitable (section 5.4.1), and if the entire course of doxycycline can be completed before 15 weeks' gestation [unlicensed].

Breast-feeding Tetracyclines should **not** be given to women who are breast-feeding (although absorption and therefore discoloration of teeth in the infant is probably usually prevented by chelation with calcium in milk).

Side-effects Side-effects of the tetracyclines include nausea, vomiting, diarrhoea (antibiotic-associated colitis reported occasionally), dysphagia, and oesophageal irritation. Other rare side-effects include hepatotoxicity, pancreatitis, blood disorders, photosensitivity (particularly with demeclocycline), and hypersensitivity reactions (including rash, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria, angioedema, anaphylaxis, pericarditis). Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment); bulging fontanelles have been reported in infants.

TETRACYCLINE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above; max. 1 g daily in divided doses

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also acute renal failure, skin discoloration

Indications and dose

Susceptible infections see notes above

• By mouth

Child 12–18 years 250 mg 4 times daily, increased in severe infections to 500 mg 3–4 times daily

Acne section 13.6.2

Non-gonococcal urethritis

• By mouth

Child 12–18 years 500 mg 4 times daily for 7–14 days (21 days if failure or relapse after first course)

Tetracycline (Non-proprietary) (PoM)

Tablets, coated, tetracycline hydrochloride 250 mg, net price 28-tab pack = £2.73. Label: 7, 9, 23, counselling, posture

Dental prescribing on NHS Tetracycline Tablets may be prescribed

DEMECLOCYCLINE HYDROCHLORIDE

Cautions see notes above, but photosensitivity more common (avoid exposure to sunlight or sun lamps)

Contra-indications see notes above

Hepatic impairment see notes above; max. 1 g daily in divided doses

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also reversible nephrogenic diabetes insipidus, acute renal failure

Indications and dose

Susceptible infections see notes above

• By mouth

Child 12–18 years 150 mg 4 times daily or 300 mg twice daily

Demeclocycline hydrochloride (Non-proprietary) (PoM)

Capsules, demeclocycline hydrochloride 150 mg, net price 28-cap pack = £81.49. Label: 7, 9, 11, 23

DOXYCYCLINE

Cautions see notes above; alcohol dependence; photosensitivity reported (avoid exposure to sunlight or sun lamps)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment use with caution (avoid excessive doses)

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also anorexia, dry mouth, flushing, anxiety, and tinnitus

Licensed use not licensed for use in children under 12 years

Indications and dose

Susceptible infections see notes above

- By mouth

Child 12–18 years 200 mg on first day, then 100 mg daily; severe infections (including refractory urinary-tract infections) 200 mg daily

Early syphilis

- By mouth

Child 12–18 years 100 mg twice daily for 14 days

Late latent syphilis

- By mouth

Child 12–18 years 100 mg twice daily for 28 days

Uncomplicated genital chlamydia, non-gonococcal urethritis, pelvic inflammatory disease Table 1, section 5.1

- By mouth

Child 12–18 years 100 mg twice daily for 7 days (14 days in pelvic inflammatory disease)

Lyme disease (see also section 5.1.1.3)

- By mouth

Child 12–18 years 100 mg twice daily for 10–14 days (for 28 days in Lyme arthritis)

Anthrax (treatment or post-exposure prophylaxis) see also section 5.1.12

- By mouth

Child under 12 years (only if alternative antibacterial cannot be given) 2.5 mg/kg twice daily (max. 100 mg twice daily)

Child 12–18 years 100 mg twice daily

Acne section 13.6.2

Adjunct to gingival scaling and root planing for periodontitis section 12.3.1

Counselling Capsules should be swallowed whole with plenty of fluid during meals while sitting or standing

Note Doxycycline doses in BNF for Children may differ from those in product literature

Doxycycline (Non-proprietary) (PoM)

Capsules, doxycycline (as hyclate) 50 mg, net price 28-cap pack = £1.50; 100 mg, 8-cap pack = £1.05.

Label: 6, 9, 11, 27, counselling, posture

Brands include Doxylar®

Dental prescribing on NHS Doxycycline Capsules 100 mg may be prescribed

Vibramycin-D® (Pfizer) (PoM)

Dispersible tablets, yellow, scored, doxycycline 100 mg, net price 8-tab pack = £4.91. Label: 6, 9, 11, 13

Dental prescribing on NHS May be prescribed as Dispersible Doxycycline Tablets

LYMECYCLINE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

Susceptible infections see notes above

- By mouth

Child 12–18 years 408 mg twice daily, increased to 1.224–1.632 g daily in severe infections

Acne

- By mouth

Child 12–18 years 408 mg daily for at least 8 weeks

Lymecycline (Non-proprietary) (PoM)

Capsules, lymecycline 408 mg (= tetracycline 300 mg), net price 28-cap pack = £4.98. Label: 6, 9

Tetralysal 300® (Galderma) (PoM)

Capsules, red/yellow, lymecycline 408 mg (= tetracycline 300 mg). Net price 28-cap pack = £4.98, 56-cap pack = £9.58. Label: 6, 9

MINOCYCLINE

Cautions see notes above; if treatment continued for longer than 6 months, monitor every 3 months for hepatotoxicity, pigmentation and for systemic lupus erythematosus—discontinue if these develop or if pre-existing systemic lupus erythematosus worsens

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment use with caution (avoid excessive doses)

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also dizziness and vertigo (more common in women); *rarely* anorexia, tinnitus, impaired hearing, hyperaesthesia, paraesthesia, acute renal failure, pigmentation (sometimes irreversible), and alopecia; *very rarely* systemic lupus erythematosus, discoloration of conjunctiva, tears, and sweat

Indications and dose

Susceptible infections see notes above

- By mouth

Child 12–18 years 100 mg twice daily

Acne section 13.6.2

Counselling Tablets or capsules should be swallowed whole with plenty of fluid while sitting or standing

Minocycline (Non-proprietary) (PoM)

Capsules, minocycline (as hydrochloride) 50 mg, net price 56-cap pack = £15.27; 100 mg, 28-cap pack = £13.09. Label: 6, 9, counselling, posture

Brands include Aknemine®

Tablets, minocycline (as hydrochloride) 50 mg, net price 28-tab pack = £5.62; 100 mg, 28-tab pack = £11.55. Label: 6, 9, counselling, posture

Modified release

Minocycline m/r preparations (PoM)

Capsules, m/r, minocycline (as hydrochloride) 100 mg, net price 56-cap pack = £20.08. Label: 6, 25

Brands include Acanamino® MR, Minocin MR®, Sebomin MR®

Dose

Acne

- By mouth

Child 12–18 years 1 capsule daily

OXYTETRACYCLINE**Cautions** see notes above**Contra-indications** see notes above**Hepatic impairment** see notes above**Renal impairment** see notes above**Pregnancy** see notes above**Breast-feeding** see notes above**Side-effects** see notes above**Indications and dose****Susceptible infections** see notes above

- By mouth

Child 12–18 years 250–500 mg 4 times daily**Acne** section 13.6.2**Oxytetracycline** (Non-proprietary) [PoM]**Tablets**, coated, oxytetracycline dihydrate 250 mg, net price 28-tab pack = £1.10. Label: 7, 9, 23**Brands include** *Oxymycin*®**Dental prescribing on NHS** Oxytetracycline Tablets may be prescribed**5.1.4 Aminoglycosides**

These include amikacin, gentamicin, neomycin, streptomycin, and tobramycin. All are bactericidal and active against some Gram-positive and many Gram-negative organisms. Amikacin, gentamicin, and tobramycin are also active against *Pseudomonas aeruginosa*; streptomycin is active against *Mycobacterium tuberculosis* and is now almost entirely reserved for tuberculosis (section 5.1.9).

The aminoglycosides are not absorbed from the gut (although there is a risk of absorption in inflammatory bowel disease and liver failure) and must therefore be given by injection for systemic infections.

The important side-effects of aminoglycosides are ototoxicity and nephrotoxicity; they occur most commonly in children with renal failure.

Gentamicin is the aminoglycoside of choice in the UK and is used widely for the treatment of serious infections. It has a broad spectrum but is inactive against anaerobes and has poor activity against haemolytic streptococci and pneumococci. When used for the 'blind' therapy of undiagnosed serious infections it is usually given in conjunction with a penicillin or metronidazole (or both). Gentamicin is used together with another antibiotic for the treatment of endocarditis (see below and Table 1, section 5.1).

Loading and maintenance doses may be calculated on the basis of the patient's weight and renal function (e.g. using a nomogram); adjustments are then made according to serum-gentamicin concentrations. High doses are occasionally indicated for serious infections, especially in the neonate, children with cystic fibrosis or the immunocompromised patient; whenever possible treatment should not exceed 7 days.

Amikacin is more stable than gentamicin to enzyme inactivation. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli.

Tobramycin has similar activity to gentamicin. It is slightly more active against *Ps. aeruginosa* but shows less activity against certain other Gram-negative bacter-

ia. Tobramycin can be administered by nebuliser or by inhalation of powder for the treatment of *Ps. aeruginosa* infection in cystic fibrosis (see Cystic Fibrosis, below).

Neomycin is too toxic for parenteral administration and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure. Oral administration may lead to malabsorption. Small amounts of neomycin may be absorbed from the gut in children with hepatic failure and, as these children may also be uraemic, cumulation may occur with resultant ototoxicity.

Cystic fibrosis A higher dose of parenteral aminoglycoside is often required in children with cystic fibrosis because renal clearance of the aminoglycoside is increased. For the role of aminoglycosides in the treatment of pseudomonal lung infections in cystic fibrosis see Table 1, section 5.1. Inhaled tobramycin is used for chronic pseudomonal lung infection in cystic fibrosis; however, resistance may develop, and some children do not respond to treatment.

NICE guidance**Tobramycin by dry powder inhalation for pseudomonal lung infection in cystic fibrosis (March 2013)**

Tobramycin dry powder for inhalation is recommended for chronic pulmonary infection caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis only if there is an inadequate response to colistimethate sodium, or if colistimethate sodium cannot be used because of contra-indications or intolerance. The manufacturer must provide tobramycin dry powder for inhalation at the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

Patients currently receiving tobramycin dry powder for inhalation can continue treatment until they, their carers, and their clinicians consider it appropriate to stop.

www.nice.org.uk/TA276

Endocarditis **Gentamicin** is used in combination with other antibiotics for the treatment of bacterial endocarditis (Table 1, section 5.1). Serum-gentamicin concentration should be determined twice each week (more often in renal impairment). **Streptomycin** may be used as an alternative in gentamicin-resistant enterococcal endocarditis.

Once daily dosage *Once daily administration* of aminoglycosides is more convenient, provides adequate serum concentrations, and has largely superseded *multiple-daily dose regimens* (given in 2–3 divided doses during the 24 hours). Local guidelines on dosage and serum concentrations should be consulted. A once-daily, high-dose regimen of an aminoglycoside should be avoided in children with endocarditis or burns of more than 20% of the total body surface area, or in children over 1 month of age with a creatinine clearance of less than 20 mL/minute/1.73m². There is insufficient evidence to recommend a once daily, high-dose regimen of an aminoglycoside in pregnancy. The *extended interval dose regimen* is used in neonates to reflect the changes in renal function that occur with increasing gestational and postnatal age (see Neonates below).

Serum concentrations Serum concentration monitoring avoids both excessive and subtherapeutic con-

centrations thus preventing toxicity and ensuring efficacy. Serum-aminoglycoside concentration should be measured in all children receiving parenteral aminoglycosides and **must** be determined in neonates, in obesity, and in cystic fibrosis, or if high doses are being given, or if there is renal impairment.

In children with normal renal function, aminoglycoside concentration should be measured initially after 3 or 4 doses of a multiple daily dose regimen; children with renal impairment may require earlier and more frequent measurement of aminoglycoside concentration.

Blood samples should be taken just before the next dose is administered ('trough' concentration). If the pre-dose ('trough') concentration is high, the interval between doses must be increased. For multiple daily dose regimens, blood samples should also be taken approximately 1 hour after intramuscular or intravenous administration ('peak' concentration). If the post-dose ('peak') concentration is high, the dose must be decreased.

Cautions The main side-effects of the aminoglycosides are dose-related, therefore, care must be taken with dosage, and, whenever possible, parenteral treatment should not exceed 7 days. Renal function should be assessed before starting an aminoglycoside and during treatment. If possible, dehydration should be corrected before starting an aminoglycoside. Auditory and vestibular function should also be monitored during treatment. In order to optimise the dose and avoid toxicity, serum-aminoglycoside concentrations should be monitored in children receiving parenteral aminoglycosides (see also Serum Concentrations).

Aminoglycosides should be used with caution in those with conditions characterised by muscular weakness (avoid in myasthenia gravis). If possible, aminoglycosides should not be given with potentially ototoxic drugs (e.g. cisplatin). Administration of an aminoglycoside and of an ototoxic diuretic (e.g. furosemide) should be separated by as long a period as practicable. **Interactions:** Appendix 1 (aminoglycosides)

Contra-indications Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis

Renal impairment Excretion of aminoglycosides is principally via the kidney and accumulation occurs in renal impairment. Ototoxicity and nephrotoxicity occur commonly in patients with renal failure. If there is impairment of renal function, the interval between doses must be increased; if the renal impairment is severe, the dose itself should be reduced as well. Serum-aminoglycoside concentrations **must** be monitored in patients with renal impairment, see Serum Concentrations above; renal, auditory, and vestibular function should also be monitored. A once-daily, high-dose regimen of an aminoglycoside should be avoided in children over 1 month of age with a creatinine clearance less than 20 mL/minute/1.73 m².

Pregnancy There is a risk of auditory or vestibular nerve damage in the infant when aminoglycosides are used in the second and third trimesters of pregnancy. The risk is greatest with streptomycin (section 5.1.9). The risk is probably very small with gentamicin and tobramycin, but their use should be avoided unless essential (if given, serum-aminoglycoside concentration monitoring is essential).

Neonates As aminoglycosides are eliminated principally via the kidney, neonatal treatment must reflect the

changes in glomerular filtration that occur with increasing gestational and postnatal age. The *extended interval dose regimen* is used in neonates, and serum-aminoglycoside concentrations **must** be measured. In patients on single daily dose regimens it may become necessary to prolong the dose interval to more than 24 hours if the trough concentration is high.

Side-effects The important side-effects of the aminoglycosides are nephrotoxicity and irreversible ototoxicity (including vestibular and auditory damage). Rash occurs commonly with streptomycin, but less frequently with the other aminoglycosides. Rare side-effects include nausea, vomiting, antibiotic-associated colitis, peripheral neuropathy, electrolyte disturbances (notably hypomagnesaemia on prolonged therapy, but also hypocalcaemia and hypokalaemia), and stomatitis. Side-effects reported very rarely include blood disorders and CNS effects (including headache, encephalopathy, and convulsions). Aminoglycosides may impair neuromuscular transmission; large doses given during surgery have been responsible for a transient myasthenic syndrome in patients with normal neuromuscular function.

GENTAMICIN

Cautions see notes above; **interactions:** Appendix 1 (aminoglycosides)

Contra-indications see notes above

Renal impairment see notes above

Pregnancy see notes above

Side-effects see notes above

Pharmacokinetics *Extended interval dose regimen in neonates:* pre-dose ('trough') concentration should be less than 2 mg/litre (less than 1 mg/litre if more than 3 doses administered); consider monitoring one hour ('peak') concentration in neonates with poor response to treatment, with oedema, with Gram-negative infection, or with birth-weight greater than 4.5 kg (consider increasing dose if 'peak' concentration less than 8 mg/litre in severe sepsis)

Once daily dose regimen: pre-dose ('trough') concentration should be less than 1 mg/litre

Multiple daily dose regimen: one hour ('peak') serum concentration should be 5–10 mg/litre (3–5 mg/litre for endocarditis, 8–12 mg/litre in cystic fibrosis); pre-dose ('trough') concentration should be less than 2 mg/litre (less than 1 mg/litre for endocarditis)

Intrathecal/intraventricular injection: cerebrospinal fluid concentration should not exceed 10 mg/litre

Indications and dose

To avoid excessive dosage in obese children, use ideal weight for height to calculate parenteral dose and monitor serum-gentamicin concentration closely

Neonatal sepsis

- Extended interval dose regimen by slow intravenous injection or intravenous infusion

Neonate less than 7 days after birth 5 mg/kg every 36 hours

Neonate more than 7 days after birth 5 mg/kg every 24 hours

Septicaemia, meningitis and other CNS infections, biliary-tract infection, acute pyelonephritis, endocarditis (see notes above), pneumonia in hospital patients, adjunct in listerial meningitis (Table 1, section 5.1)

- Once daily dose regimen (not for endocarditis or meningitis) by intravenous infusion

Child 1 month–18 years initially 7 mg/kg, then adjusted according to serum-gentamicin concentration

- Multiple daily dose regimen by intramuscular or by slow intravenous injection over at least 3 minutes

Child 1 month–12 years 2.5 mg/kg every 8 hours

Child 12–18 years 2 mg/kg every 8 hours

Pseudomonal lung infection in cystic fibrosis

- Multiple daily dose regimen by slow intravenous injection over at least 3 minutes or by intravenous infusion

Child 1 month–18 years 3 mg/kg every 8 hours

Bacterial ventriculitis and CNS infection (supplement to systemic therapy)

- By intrathecal or intraventricular injection, seek specialist advice

Neonate seek specialist advice

Child 1 month–18 years 1 mg daily (increased if necessary to 5 mg daily)

Note only preservative-free, intrathecal preparation should be used

Eye section 11.3.1

Ear section 12.1.1

Note Local guidelines may vary

Administration for *intravenous infusion*, dilute in Glucose 5% or Sodium Chloride 0.9%; give over 30 minutes

For *nebulisation*, dilute preservative-free preparation in 3 mL sodium chloride 0.9%. Administer after physiotherapy and bronchodilators

For *intrathecal or intraventricular injection*, use preservative-free intrathecal preparations only

Gentamicin (Non-proprietary) (PoM)

Injection, gentamicin (as sulfate), net price 40 mg/mL, 1-mL amp = £1.40, 2-mL amp = £1.54, 2-mL vial = £4.00

Paediatric injection, gentamicin (as sulfate) 10 mg/mL, net price 2-mL vial = £2.25

Intrathecal injection, gentamicin (as sulfate) 5 mg/mL, net price 1-mL amp = 74p

Intravenous infusion, gentamicin (as sulfate) 1 mg/mL in sodium chloride intravenous infusion 0.9%, net price 80-mL (80 mg) bottle = £1.95; 3 mg/mL, 80-mL (240 mg) bottle = £5.95, 120-mL (360 mg) bottle = £8.45

Cidomycin® (Sanofi-Aventis) (PoM)

Injection, gentamicin (as sulfate) 40 mg/mL. Net price 2-mL amp or vial = £1.38

Genticin® (AMCo) (PoM)

Injection, gentamicin (as sulfate) 40 mg/mL. Net price 2-mL amp = £1.00

Isotonic Gentamicin Injection (Baxter) (PoM)

Intravenous infusion, gentamicin (as sulfate) 800 micrograms/mL in sodium chloride intravenous infusion 0.9%. Net price 100-mL (80-mg) *Viaflex*® bag = £1.61

Electrolytes Na⁺ 15.4 mmol/100-mL bag

AMIKACIN

Cautions see notes above; **interactions:** Appendix 1 (aminoglycosides)

Contra-indications see notes above

Renal impairment see notes above

Pregnancy see notes above

Side-effects see notes above

Pharmacokinetics *Multiple dose regimen:* one-hour ('peak') serum concentration should not exceed 30 mg/litre; pre-dose ('trough') concentration should be less than 10 mg/litre

Once daily dose regimen: pre-dose ('trough') concentration should be less than 5 mg/litre

Licensed use dose for cystic fibrosis not licensed

Indications and dose

To avoid excessive dosage in obese children, use ideal weight for height to calculate dose and monitor serum-amikacin concentration closely

Neonatal sepsis

- Extended interval dose regimen by slow intravenous injection over 3–5 minutes or by intravenous infusion

Neonate 15 mg/kg every 24 hours

- Multiple daily dose regimen by intramuscular or by slow intravenous injection or by infusion

Neonate loading dose of 10 mg/kg then 7.5 mg/kg every 12 hours

Serious Gram-negative infections resistant to gentamicin

- By slow intravenous injection over 3–5 minutes

Child 1 month–12 years 7.5 mg/kg every 12 hours

Child 12–18 years 7.5 mg/kg every 12 hours, increased to 7.5 mg/kg every 8 hours in severe infections, max. 500 mg every 8 hours for up to 10 days (max. cumulative dose 15 g)

Once daily dose regimen (not for endocarditis or meningitis)

- By intravenous injection or infusion

Child 1 month–18 years initially 15 mg/kg, then adjusted according to serum-amikacin concentration

Pseudomonal lung infection in cystic fibrosis

- Multiple daily dose regimen by slow intravenous injection or infusion

Child 1 month–18 years 10 mg/kg every 8 hours (max. 500 mg every 8 hours)

Note Local dosage guidelines may vary

Administration for *intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%; give over 30–60 minutes

Amikacin (Non-proprietary) (PoM)

Injection, amikacin (as sulfate) 250 mg/mL. Net price 2-mL vial = £9.64

Electrolytes Na^+ 0.56 mmol/500-mg vial

Amikin® (Bristol-Myers Squibb) (PoM)

Injection, amikacin (as sulfate) 50 mg/mL. Net price 2-mL vial = £2.07

Electrolytes Na^+ < 0.5 mmol/vial

TOBRAMYCIN

Cautions see notes above ; **interactions**: Appendix 1 (aminoglycosides)

Specific cautions for inhaled treatment Other inhaled drugs should be administered before tobramycin. Measure lung function before and after initial dose of tobramycin and monitor for bronchospasm; if bronchospasm occurs in a child not using a bronchodilator, repeat test using bronchodilator. Monitor renal function before treatment and then annually. Severe haemoptysis—risk of further haemorrhage

Contra-indications see notes above

Renal impairment see notes above

Pregnancy see notes above

Side-effects see notes above; *on inhalation*, cough (more frequent by inhalation of powder), bronchospasm (see Cautions), dysphonia, taste disturbances, pharyngitis, mouth ulcers, salivary hypersecretion, laryngitis, haemoptysis, epistaxis

Pharmacokinetics *Extended interval dose regimen in neonates*: pre-dose ('trough') concentration should be less than 2 mg/litre

Once daily dose regimen: pre-dose ('trough') concentration should be less than 1 mg/litre

Multiple daily dose regimen: one-hour ('peak') serum concentration should not exceed 10 mg/litre (8–12 mg/litre in cystic fibrosis); pre-dose ('trough') concentration should be less than 2 mg/litre

Indications and dose

To avoid excessive dosage in obese children, use ideal weight for height to calculate parenteral dose and monitor serum-tobramycin concentration closely

Neonatal sepsis

- Extended interval dose regimen by intravenous injection over 3–5 minutes or by intravenous infusion

Neonate less than 32 weeks corrected gestational age 4–5 mg/kg every 36 hours

Neonate 32 weeks and over corrected gestational age 4–5 mg/kg every 24 hours

- Multiple daily dose regimen by slow intravenous injection or by intravenous infusion

Neonate under 7 days 2 mg/kg every 12 hours

Neonate 7–28 days 2–2.5 mg/kg every 8 hours

Septicaemia, meningitis and other CNS infections, biliary-tract infection, acute pyelonephritis, pneumonia in hospital patients

- Multiple daily dose regimen by slow intravenous injection over 3–5 minutes

Child 1 month–12 years 2–2.5 mg/kg every 8 hours

Child 12–18 years 1 mg/kg every 8 hours; in severe infections up to 5 mg/kg daily in divided doses every 6–8 hours (reduced to 3 mg/kg daily as soon as clinically indicated)

- Once daily dose regimen by intravenous infusion

Child 1 month–18 years initially 7 mg/kg, then adjusted according to serum-tobramycin concentration

Pseudomonal lung infection in cystic fibrosis

- Multiple daily dose regimen by slow intravenous injection over 3–5 minutes

Child 1 month–18 years 8–10 mg/kg/daily in 3 divided doses

- Once daily dose regimen by intravenous infusion over 30 minutes

Child 1 month–18 years initially 10 mg/kg (max. 660 mg), then adjusted according to serum-tobramycin concentration

Chronic pulmonary *Pseudomonas aeruginosa* infection in patients with cystic fibrosis

- By inhalation of nebulised solution

Child 6–18 years 300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution

- By inhalation of powder

Child 6–18 years 112 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin inhalation powder

Note Local dosage guidelines may vary

Administration for *intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%; give over 20–60 minutes

Parenteral

Tobramycin (Non-proprietary) (PoM)

Injection, tobramycin (as sulfate) 40 mg/mL, net price 1-mL (40-mg) vial = £3.70, 2-mL (80-mg) vial = £3.77, 6-mL (240-mg) vial = £45.00

Inhalation

Bramitob® (Chiesi) (PoM)

Nebuliser solution, tobramycin 75 mg/mL, net price 56 x 4-mL (300-mg) unit = £1187.00

Tobi® (Novartis) (PoM)

Nebuliser solution, tobramycin 60 mg/mL, net price 56 x 5-mL (300-mg) unit = £1187.20

Podhaler (dry powder for inhalation), tobramycin 28 mg/capsule, net price 56-cap pack (with *Tobi®* Podhaler device) = £447.50, 224-cap pack (with 5 *Tobi®* Podhaler devices) = £1790.00. Counselling, administration

5.1.5 Macrolides

The macrolides have an antibacterial spectrum that is similar but not identical to that of penicillin; they are thus an alternative in penicillin-allergic patients. They are active against many-penicillin-resistant staphylococci, but some are now also resistant to the macrolides.

Indications for the macrolides include campylobacter enteritis, respiratory infections (including pneumonia, whooping cough, Legionella, chlamydia, and mycoplasma infection), and skin infections.

Erythromycin is also used in the treatment of early syphilis, uncomplicated genital chlamydial infection, and non-gonococcal urethritis. Erythromycin has poor activity against *Haemophilus influenzae*. Erythromycin causes nausea, vomiting, and diarrhoea in some patients; in mild to moderate infections this can be avoided by giving a lower dose or the total dose in 4 divided doses, but if a more serious infection, such as *Legionella pneumoniae*, is suspected higher doses are needed.

Azithromycin is a macrolide with slightly less activity than erythromycin against Gram-positive bacteria, but enhanced activity against some Gram-negative organisms including *H. influenzae*. Plasma concentrations are very low, but tissue concentrations are much higher. It has a long tissue half-life and once daily dosage is recommended. Azithromycin is also used in the treatment of uncomplicated genital chlamydial infection, non-gonococcal urethritis, typhoid [unlicensed indication], and trachoma [unlicensed indication] (section 11.3.1).

Clarithromycin is an erythromycin derivative with slightly greater activity than the parent compound. Tissue concentrations are higher than with erythromycin. It is given twice daily. Clarithromycin is also used in regimens for *Helicobacter pylori* eradication (section 1.3).

For the role of erythromycin, azithromycin, and clarithromycin in the treatment of Lyme disease, see section 5.1.1.3.

Spiramycin is also a macrolide (section 5.4.7).

Oral infections The macrolides are an alternative for oral infections in penicillin-allergic patients or where a beta-lactamase producing organism is involved. However, many organisms are now resistant to macrolides or rapidly develop resistance; their use should therefore be limited to short courses. Metronidazole (section 5.1.11) may be preferred as an alternative to a penicillin.

Cautions Macrolides should be used with caution in children with a predisposition to QT interval prolongation (including electrolyte disturbances and concomitant use of drugs that prolong the QT interval). Macrolides may aggravate myasthenia gravis. **Interactions:** Appendix 1 (macrolides)

Side-effects Nausea, vomiting, abdominal discomfort, and diarrhoea are the most common side-effects of the macrolides, but they are mild and less frequent with azithromycin and clarithromycin than with erythromycin. Hepatotoxicity (including cholestatic jaundice) and rash occur less frequently. Other side-effects reported rarely or very rarely include pancreatitis, antibiotic-associated colitis, QT interval prolongation, arrhythmias, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Generally reversible hearing loss (sometimes with tinnitus) can occur after large doses of a macrolide; it occurs commonly after long-term therapy with azithromycin. Intravenous infusion may cause local tenderness and phlebitis.

AZITHROMYCIN

Cautions see notes above; **interactions:** Appendix 1 (macrolides)

Hepatic impairment manufacturers advise avoid in severe liver disease—no information available

Renal impairment use with caution if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy manufacturers advise use only if adequate alternatives not available

Breast-feeding present in milk; use only if no suitable alternative

Side-effects see notes above; also anorexia, dyspepsia, flatulence, dizziness, headache, malaise, paraesthesia, arthralgia, disturbances in taste and vision; *less commonly* constipation, gastritis, chest pain, oedema, anxiety, sleep disturbances, hypoaesthesia, leucopenia, photosensitivity; *rarely* agitation; also reported syncope, convulsions, smell disturbances, interstitial nephritis, acute renal failure, thrombocytopenia, haemolytic anaemia, tongue discoloration

Licensed use not licensed for typhoid fever, Lyme disease, chronic *Pseudomonas aeruginosa* infection in cystic fibrosis, or prophylaxis of group A streptococcal infection

Indications and dose

Respiratory-tract infections, otitis media, skin and soft-tissue infections

• By mouth

Child over 6 months 10 mg/kg once daily (max. 500 mg once daily) for 3 days

or

Body-weight 15–25 kg 200 mg once daily for 3 days

Body-weight 26–35 kg 300 mg once daily for 3 days

Body-weight 36–45 kg 400 mg once daily for 3 days

Body-weight over 45 kg 500 mg once daily for 3 days

Infection in cystic fibrosis

• By mouth

Child 6 months–18 years 10 mg/kg once daily (max. 500 mg once daily) for 3 days; course repeated after 1 week, then repeat as necessary

Chronic *Pseudomonas aeruginosa* infection in cystic fibrosis

• By mouth

Child 6–18 years

Body-weight 25–40 kg 250 mg 3 times a week

Body-weight over 40 kg 500 mg 3 times a week

Uncomplicated genital chlamydial infections and non-gonococcal urethritis

• By mouth

Child 12–18 years 1 g as a single dose

Lyme disease (see also section 5.1.1.3), mild to moderate typhoid due to multiple-antibacterial resistant organisms

• By mouth

Child 6 months–18 years 10 mg/kg once daily (max. 500 mg) for 7–10 days (for 7 days in typhoid)

Prevention of group A streptococcal infection

Table 2, section 5.1

Azithromycin (Non-proprietary) (PoM)

Capsules, azithromycin (as dihydrate) 250 mg, net price 4-cap pack = £9.79, 6-cap pack = £14.81. Label: 5, 9, 23

Dental prescribing on NHS Azithromycin Capsules may be prescribed

Tablets, azithromycin (as monohydrate hemi-ethanolate) 250 mg, net price 4-tab pack = £2.17; 500 mg, 3-tab pack = £1.74. Label: 5, 9

Dental prescribing on NHS Azithromycin Tablets may be prescribed

Note Azithromycin tablets can be sold to the public for the treatment of confirmed, asymptomatic *Chlamydia trachomatis* genital infection in those over 16 years of age, and for the epidemiological treatment of their sexual partners, subject to max. single dose of 1 g, max. daily dose 1 g, and a pack size of 1 g

Oral suspension, azithromycin (as monohydrate) 200 mg/5 mL when reconstituted with water, net price 15-mL pack = £4.06, 30-mL pack = £11.04. Label: 5, 9

Dental prescribing on NHS Azithromycin Oral Suspension 200 mg/5 mL may be prescribed

Zithromax® (Pfizer) (PoM)

Capsules, azithromycin (as dihydrate) 250 mg, net price 4-cap pack = £7.16, 6-cap pack = £10.74. Label: 5, 9, 23

Oral suspension, cherry/banana-flavoured, azithromycin (as dihydrate) 200 mg/5 mL when reconstituted with water. Net price 15-mL pack = £4.06, 22.5-mL pack = £6.10, 30-mL pack = £11.04. Label: 5, 9

CLARITHROMYCIN

Cautions see notes above; **interactions:** Appendix 1 (macrolides)

Hepatic impairment hepatic dysfunction including jaundice reported; avoid in severe impairment if renal impairment is also present

Renal impairment use half normal dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m², max. duration 14 days; avoid *Klaricid XL®* or clarithromycin m/r preparations if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid, particularly in the first trimester, unless potential benefit outweighs risk

Breast-feeding manufacturer advises avoid unless potential benefit outweighs risk—present in milk

Side-effects see notes above; also dyspepsia, taste disturbances, headache, insomnia, hyperhidrosis; less commonly gastritis, flatulence, constipation, dry mouth, stomatitis, glossitis, anorexia, chest pain, anxiety, dizziness, tremor, malaise, blood disorders (including leucopenia), myalgia, tinnitus; also reported confusion, psychotic disorders, depression, abnormal dreams, convulsions, paraesthesia, hypoglycaemia, renal failure, interstitial nephritis, myopathy, tooth and tongue discoloration, smell disturbances

Licensed use tablets and intravenous infusion not licensed for use in children under 12 years; oral suspension not licensed for use in infants under 6 months

Indications and dose

Respiratory-tract infections, mild to moderate skin and soft-tissue infections, otitis media (see also Table 1, section 5.1)

● By mouth

Neonate 7.5 mg/kg twice daily

Child 1 month–12 years

Body-weight under 8 kg 7.5 mg/kg twice daily

Body-weight 8–11 kg 62.5 mg twice daily

Body-weight 12–19 kg 125 mg twice daily

Body-weight 20–29 kg 187.5 mg twice daily

Body-weight 30–40 kg 250 mg twice daily

Child 12–18 years 250 mg twice daily, increased if necessary in severe infections to 500 mg twice daily; usual duration 7–14 days

● By intravenous infusion into large proximal vein

Child 1 month–12 years 7.5 mg/kg (max. 500 mg) every 12 hours

Child 12–18 years 500 mg every 12 hours

Lyme disease (see also section 5.1.1.3)

● By mouth

Child 1 month–12 years 7.5 mg/kg (max. 500 mg) twice daily for 14–21 days

Child 12–18 years 500 mg twice daily for 14–21 days

Helicobacter pylori eradication section 1.3

Prevention of pertussis Table 2, section 5.1

Administration for intermittent intravenous infusion dilute reconstituted solution further in Glucose 5% or Sodium chloride 0.9% to a concentration of 2 mg/mL; give into large proximal vein over 60 minutes

Clarithromycin (Non-proprietary) (PoM)

Tablets, clarithromycin 250 mg, net price 14-tab pack = £1.64; 500 mg, 14-tab pack = £2.63. Label: 9

Dental prescribing on NHS Clarithromycin Tablets may be prescribed

Oral suspension, clarithromycin for reconstitution with water 125 mg/5 mL, net price 70 mL = £4.05; 250 mg/5 mL, 70 mL = £6.91. Label: 9

Dental prescribing on NHS Clarithromycin Oral Suspension may be prescribed

Intravenous infusion, powder for reconstitution, clarithromycin; net price 500-mg vial = £9.45

Klaricid® (Abbott Healthcare) (PoM)

Tablets, both yellow, f/c, clarithromycin 250 mg, net price 14-tab pack = £7.00; 500 mg, 14-tab pack = £11.30, 20-tab pack = £16.15. Label: 9

Paediatric suspension, clarithromycin for reconstitution with water 125 mg/5 mL, net price 70 mL = £5.26, 100 mL = £9.04; 250 mg/5 mL, 70 mL = £10.51. Label: 9

Granules, clarithromycin 250 mg/sachet, net price 14-sachet pack = £11.68. Label: 9, 13

Intravenous infusion, powder for reconstitution, clarithromycin. Net price 500-mg vial = £9.45

Electrolytes Na⁺ < 0.5 mmol/500-mg vial

Modified release

Clarithromycin m/r preparations (PoM)

Tablets, m/r, clarithromycin 500 mg, net price 7 = £6.72, 14 = £13.23. Label: 9, 21, 25

Brands include Mycifor XL®

Dose

- By mouth

Child 12–18 years 500 mg once daily (doubled in severe infections) for 7–14 days

Klaricid XL® (Abbott Healthcare) (PoM)

Tablets, m/r, yellow, clarithromycin 500 mg, net price 7-tab pack = £6.72, 14-tab pack = £13.23.

Label: 9, 21, 25

Dose

- By mouth

Child 12–18 years 500 mg once daily (doubled in severe infections) for 7–14 days

ERYTHROMYCIN

Cautions see notes above; neonate under 2 weeks (risk of hypertrophic pyloric stenosis); avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (macrolides)

Hepatic impairment may cause idiosyncratic hepatotoxicity

Renal impairment reduce dose in severe renal impairment (ototoxicity)

Pregnancy not known to be harmful

Breast-feeding only small amounts in milk—not known to be harmful

Side-effects see notes above

Indications and dose

Susceptible infections in patients with penicillin hypersensitivity, oral infections (see notes above), campylobacter enteritis, respiratory-tract infections (including Legionella infection), skin infections, chlamydial ophthalmia, prevention and treatment of pertussis (see also Table 2, section 5.1)

- By mouth

Neonate 12.5 mg/kg every 6 hours

Child 1 month–2 years 125 mg 4 times daily; dose doubled in severe infections

Child 2–8 years 250 mg 4 times daily; dose doubled in severe infections

Child 8–18 years 250–500 mg 4 times daily; dose doubled in severe infections

Note Total daily dose may be given in two divided doses

- By intravenous infusion

Neonate 10–12.5 mg/kg every 6 hours

Child 1 month–18 years 12.5 mg/kg (max. 1 g) every 6 hours

Early syphilis

- By mouth

Child 12–18 years 500 mg 4 times daily for 14 days

Uncomplicated genital chlamydia, non-gonococcal urethritis, pelvic inflammatory disease (see also Table 1, section 5.1)

- By mouth

Child 1 month–2 years 12.5 mg/kg 4 times daily for 14 days

Child 2–12 years 250 mg twice daily for 14 days

Child 12–18 years 500 mg twice daily for 14 days

Lyme disease (see also section 5.1.1.3)

- By mouth

Child 1 month–18 years 12.5 mg/kg (max. 500 mg) 4 times daily for 14–21 days

Prophylaxis against pneumococcal infection

Table 2, section 5.1

Gastric stasis section 1.2

Acne vulgaris section 13.6

Diphtheria prophylaxis Table 2, section 5.1

Prevention of group A streptococcal infection

Table 2, section 5.1

Administration Dilute reconstituted solution further in glucose 5% (neutralised with Sodium bicarbonate) or sodium chloride 0.9% to a concentration of 1–5 mg/mL; give over 20–60 minutes. Concentration of up to 10 mg/mL may be used in fluid-restriction if administered via a central venous catheter

Erythromycin (Non-proprietary) (PoM)

Capsules, enclosing e/c microgranules, erythromycin 250 mg, net price 28-cap pack = £5.61. Label: 5, 9, 25

Brands include Tilorith®

Tablets, e/c, erythromycin 250 mg, net price 28 = £1.61. Label: 5, 9, 25

Dental prescribing on NHS Erythromycin Tablets e/c may be prescribed

Erythromycin Ethyl Succinate (Non-proprietary) (PoM)

Oral suspension, erythromycin (as ethyl succinate) for reconstitution with water 125 mg/5 mL, net price 100 mL = £2.79; 250 mg/5 mL, 100 mL = £4.20; 500 mg/5 mL, 100 mL = £7.14. Label: 9

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Brands include Primacine®

Dental prescribing on NHS Erythromycin Ethyl Succinate Oral Suspension may be prescribed

Erythromycin Lactobionate (Non-proprietary) (PoM)

Intravenous infusion, powder for reconstitution, erythromycin (as lactobionate), net price 1-g vial = £10.98

Erymax® (TEVA UK) (PoM)

Capsules, opaque orange/clear orange, enclosing orange and white e/c pellets, erythromycin 250 mg, net price 28-cap pack = £5.61, 112-cap pack = £22.44. Label: 5, 9, 25

Erythrocin® (AMCo) (PoM)

Tablets, both f/c, erythromycin (as stearate), 250 mg, net price 100-tab pack = £18.20; 500 mg, 100-tab pack = £36.40. Label: 9

Dental prescribing on NHS May be prescribed as Erythromycin Stearate Tablets

Erythroped® (AMCo) (PoM)

Suspension SF, sugar-free, banana-flavoured, erythromycin (as ethyl succinate) for reconstitution with water, 125 mg/5 mL (*Suspension PI SF*), net price 140 mL = £3.06; 250 mg/5 mL, 140 mL = £5.95; 500 mg/5 mL (*Suspension SF Forte*), 140 mL = £10.56. Label: 9

Erythroped A® (AMCo) (PoM)

Tablets, yellow, f/c, erythromycin 500 mg (as ethyl succinate). Net price 28-tab pack = £10.78. Label: 9

Dental prescribing on NHS May be prescribed as Erythromycin Ethyl Succinate Tablets

5.1.6 Clindamycin

Clindamycin is active against Gram-positive cocci, including streptococci and penicillin-resistant staphylococci, and also against many anaerobes, especially *Bacteroides fragilis*. It is well concentrated in bone and excreted in bile and urine.

Clindamycin is recommended for staphylococcal joint and bone infections such as osteomyelitis, and intra-abdominal sepsis; it is an alternative to macrolides for erysipelas or cellulitis in penicillin-allergic patients. It is also used in combination with other antibacterials for cellulitis in immunocompromised children. Clindamycin can also be used for infections associated with methicillin-resistant *Staphylococcus aureus* (MRSA) in bone and joint infections, and skin and soft-tissue infections.

Clindamycin has been associated with antibiotic-associated colitis (section 1.5), which may be fatal. Although it can occur with most antibacterials, antibiotic-associated colitis occurs more frequently with clindamycin. Children should therefore discontinue treatment immediately if diarrhoea develops.

Oral infections Clindamycin should not be used routinely for the treatment of oral infections because it may be no more effective than penicillins against anaerobes and there may be cross-resistance with erythromycin-resistant bacteria. Clindamycin can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or to metronidazole.

CLINDAMYCIN

Cautions discontinue immediately if diarrhoea or colitis develops; monitor liver and renal function if treatment exceeds 10 days, and in neonates and infants; avoid rapid intravenous administration; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (clindamycin)

Contra-indications diarrhoeal states; avoid injections containing benzyl alcohol in neonates (see under preparations below)

Pregnancy not known to be harmful

Breast-feeding amount probably too small to be harmful; bloody diarrhoea reported in 1 infant

Side-effects diarrhoea (discontinue treatment), abdominal discomfort, oesophagitis, oesophageal ulcers, taste disturbances, nausea, vomiting, antibiotic-associated colitis; jaundice; leucopenia, eosinophilia, and thrombocytopenia reported; polyarthritides reported; rash, pruritus, urticaria, anaphylactoid reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative and vesiculobullous dermatitis reported; pain, induration, and abscess after intramuscular injection; thrombophlebitis after intravenous injection

Indications and dose

Staphylococcal bone and joint infections, peritonitis see notes above

• By mouth

Neonate under 14 days 3–6 mg/kg 3 times daily

Neonate 14–28 days 3–6 mg/kg 4 times daily

Child 1 month–18 years 3–6 mg/kg (max. 450 mg) 4 times daily

• By deep intramuscular injection or by intravenous infusion

Child 1 month–18 years 3.75–6.25 mg/kg 4 times daily; increased up to 10 mg/kg (max. 1.2 g) 4 times daily in severe infections; total daily dose may alternatively be given in 3 divided doses; single doses above 600 mg by intravenous infusion only; single doses by intravenous infusion not to exceed 1.2 g

Staphylococcal lung infection in cystic fibrosis

• By mouth

Child 1 month–18 years 5–7 mg/kg (max. 600 mg) 4 times daily

Treatment of falciparum malaria, see p. 334

Administration for intravenous infusion, dilute to a concentration of not more than 18 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 10–60 minutes at a max. rate of 20 mg/kg/hour

Clindamycin (Non-proprietary) [PoM]

Capsules, clindamycin (as hydrochloride) 150 mg, net price 24-cap pack = £5.08. Label: 9, 27, counselling, see above (diarrhoea)

Dental prescribing on NHS Clindamycin Capsules may be prescribed

Injection, clindamycin (as phosphate) 150 mg/mL, net price 2-mL amp = £5.90, 4-mL amp = £11.80

Liquid, 75 mg/5 mL available from 'special-order' manufacturers or specialist importing companies, see p. 840

Dalacin C[®] (Pharmacia) [PoM]

Capsules, clindamycin (as hydrochloride) 75 mg (green/white), net price 24-cap pack = £7.45; 150 mg, (white), 24-cap pack = £13.72. Label: 9, 27, counselling, see above (diarrhoea)

Dental prescribing on NHS May be prescribed as Clindamycin Capsules

Injection, clindamycin (as phosphate) 150 mg/mL, net price 2-mL amp = £6.20, 4-mL amp = £12.35

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

5.1.7 Some other antibacterials

Antibacterials discussed in this section include chloramphenicol, fusidic acid, glycopeptide antibiotics (vancomycin and teicoplanin), linezolid, and the polymyxin, colistimethate sodium.

Chloramphenicol

Chloramphenicol is a potent broad-spectrum antibiotic; however, it is associated with serious haematological side-effects when given systemically and should therefore be reserved for the treatment of life-threatening infections, particularly those caused by *Haemophilus influenzae*, and also for typhoid fever. Chloramphenicol is also used in cystic fibrosis for the treatment of respiratory *Burkholderia cepacia* infection resistant to other antibacterials.

Grey baby syndrome may follow excessive doses in neonates with immature hepatic metabolism; monitoring of plasma concentrations is recommended.

Chloramphenicol eye drops (section 11.3.1) and chloramphenicol ear drops (section 12.1.1) are also available.

CHLORAMPHENICOL

Cautions avoid repeated courses and prolonged treatment; blood counts required before and periodically during treatment; monitor plasma-chloramphenicol concentration in neonates (see below); **interactions:** Appendix 1 (chloramphenicol)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment avoid if possible—increased risk of bone-marrow depression; reduce dose and monitor plasma-chloramphenicol concentration

Renal impairment avoid in severe impairment unless no alternative; dose-related depression of haematopoiesis

Pregnancy manufacturer advises avoid; neonatal grey-baby syndrome if used in third trimester

Breast-feeding manufacturer advises avoid; use another antibiotic; may cause bone-marrow toxicity in infant; concentration in milk usually insufficient to cause 'grey-baby syndrome'

Side-effects blood disorders including reversible and irreversible aplastic anaemia (with reports of resulting leukaemia), peripheral neuritis, optic neuritis, headache, depression, urticaria, erythema multiforme, nausea, vomiting, diarrhoea, stomatitis, glossitis, dry mouth; nocturnal haemoglobinuria reported; grey syndrome (abdominal distension, pallid cyanosis, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism (see Pharmacokinetics below)

Pharmacokinetics plasma concentration monitoring required in neonates and preferred in those under 4 years of age, and in hepatic impairment; recommended peak plasma concentration (approx. 2 hours after administration by mouth, intravenous injection or infusion) 10–25 mg/litre; pre-dose ('trough') concentration should not exceed 15 mg/litre

Indications and dose

See notes above

- By intravenous injection

Neonate up to 14 days 12.5 mg/kg twice daily

Neonate 14–28 days 12.5 mg/kg 2–4 times daily

Note Check dosage carefully; overdosage can be fatal (see also pharmacokinetics above)

- By mouth or by intravenous injection or infusion

Child 1 month–18 years 12.5 mg/kg every 6 hours; dose may be doubled in severe infections such as septicaemia, meningitis and epiglottitis providing plasma-chloramphenicol concentrations are measured and high doses reduced as soon as indicated

Administration Displacement value may be significant for injection, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9%

Chloramphenicol (Non-proprietary) (PoM)

Capsules, chloramphenicol 250 mg. Net price 60 = £377.00

Kemeticine[®] (Pharmacia) (PoM)

Injection, powder for reconstitution, chloramphenicol (as sodium succinate). Net price 1-g vial = £1.39

Electrolytes Na⁺ 3.14 mmol/g

Fusidic acid

Fusidic acid and its salts are narrow-spectrum antibiotics. The only indication for their use is in infections caused by penicillin-resistant staphylococci, especially osteomyelitis, as they are well concentrated in bone; they are also used for staphylococcal endocarditis. A second antistaphylococcal antibiotic is usually required to prevent emergence of resistance during treatment.

SODIUM FUSIDATE

Cautions monitor liver function with high doses or on prolonged therapy; elimination may be reduced in hepatic impairment or biliary disease or biliary obstruction; **interactions:** Appendix 1 (fusidic acid)

Hepatic impairment impaired biliary excretion, avoid or reduce dose; possibly increased risk of hepatotoxicity, monitor liver function

Pregnancy not known to be harmful; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding present in milk; manufacturer advises caution

Side-effects nausea, vomiting, abdominal pain, dyspepsia, diarrhoea, drowsiness, dizziness; *less commonly* anorexia, headache, malaise, rash, pruritus; also reported, reversible jaundice especially after high dosage (withdraw therapy if persistent), acute renal failure (usually with jaundice), blood disorders

Indications and dose

Penicillin-resistant staphylococcal infection including osteomyelitis, staphylococcal endocarditis in combination with other antibacterials see under Preparations, below

Fucidin[®] (LEO) (PoM)

Tablets, f/c, sodium fusidate 250 mg, net price 10-tab pack = £6.02. Label: 9

Dose

As sodium fusidate

- By mouth

Child 12–18 years 500 mg every 8 hours, dose doubled for severe infections

Skin infection as sodium fusidate

- By mouth

Child 12–18 years 250 mg every 12 hours for 5–10 days

Suspension, off-white, banana- and orange-flavoured, fusidic acid 250 mg/5 mL, net price 50 mL = £6.73. Label: 9, 21

Dose

As fusidic acid

- By mouth

Neonate 15 mg/kg 3 times daily

Child 1 month–1 year 15 mg/kg 3 times daily

Child 1–5 years 250 mg 3 times daily

Child 5–12 years 500 mg 3 times daily

Child 12–18 years 750 mg 3 times daily

Note Fusidic acid is incompletely absorbed and doses recommended for suspension are proportionately higher than those for sodium fusidate tablets

Vancomycin and teicoplanin

The glycopeptide antibiotics **vancomycin** and **teicoplanin** have bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resis-

tant staphylococci. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides. There are increasing reports of glycopeptide-resistant *Enterococci*.

They are used *parenterally* in the treatment of serious infections caused by Gram-positive cocci. Teicoplanin is similar to vancomycin, but has a significantly longer duration of action, allowing once daily administration after the loading dose. Teicoplanin is associated with a lower incidence of nephrotoxicity than vancomycin.

They are also used for surgical prophylaxis when there is a high risk of MRSA (Table 2, section 5.1).

Penetration in to cerebrospinal fluid is poor; vancomycin may be administered by the *intrathecal* or *intraventricular* route for treatment of meningitis [unlicensed].

Vancomycin (added to dialysis fluid) is also used in the treatment of peritonitis associated with peritoneal dialysis [unlicensed route] (Table 1, section 5.1).

Vancomycin given *by mouth* for 10–14 days is effective in the treatment of *Clostridium difficile* infection (see also section 1.5); low doses are considered adequate (higher dose may be considered if the infection fails to respond or if it is life-threatening). Vancomycin should **not** be given by mouth for systemic infections since it is not significantly absorbed.

VANCOMYCIN

Cautions avoid rapid infusion (risk of anaphylactoid reactions, see Side-effects); rotate infusion sites; avoid if history of deafness; all patients require plasma-vancomycin measurement (after 3 or 4 doses if renal function normal, earlier if renal impairment), blood counts, urinalysis, and renal function tests; monitor auditory function in renal impairment; teicoplanin sensitivity; systemic absorption may follow oral administration especially in inflammatory bowel disorders or following multiple doses; **interactions:** Appendix 1 (vancomycin)

Specific cautions for inhaled treatment Administer inhaled bronchodilator before vancomycin. Measure lung function before and after initial dose of vancomycin and monitor for bronchospasm.

Renal impairment reduce dose—monitor plasma-vancomycin concentration and renal function regularly; see also Cautions above

Pregnancy manufacturer advises use only if potential benefit outweighs risk—plasma-vancomycin concentration monitoring essential to reduce risk of fetal toxicity

Breast-feeding present in milk—significant absorption following oral administration unlikely

Side-effects after parenteral administration: nephrotoxicity including renal failure and interstitial nephritis; ototoxicity (discontinue if tinnitus occurs); blood disorders including neutropenia (usually after 1 week or high cumulative dose), rarely agranulocytosis and thrombocytopenia; nausea; chills; fever; eosinophilia, anaphylaxis, rashes (including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis); phlebitis (irritant to tissue); on rapid infusion, severe hypotension (including shock and cardiac arrest), wheezing, dyspnoea, urticaria, pruritus, flushing of the upper body ('red man' syndrome), pain and muscle spasm of back and chest

Pharmacokinetics plasma concentration monitoring required; pre-dose ('trough') concentration should be 10–15 mg/litre (15–20 mg/litre for less sensitive strains of methicillin-resistant *Staphylococcus aureus*)

Licensed use not licensed for intraventricular use or inhalation

Indications and dose

Infections due to Gram-positive bacteria including osteomyelitis, septicaemia and soft-tissue infections see notes above

• By intravenous infusion

Neonate less than 29 weeks corrected gestational age 15 mg/kg every 24 hours, adjusted according to plasma concentration

Neonate 29–35 weeks corrected gestational age 15 mg/kg every 12 hours, adjusted according to plasma concentration

Neonate over 35 weeks corrected gestational age 15 mg/kg every 8 hours, adjusted according to plasma concentration

Child 1 month–18 years 15 mg/kg every 8 hours (maximum daily dose 2 g), adjusted according to plasma concentration

***Clostridium difficile* infection** (see also notes above)

• By mouth

Child 1 month–5 years 5 mg/kg 4 times daily for 10–14 days (increased up to 10 mg/kg 4 times daily if infection fails to respond or is life-threatening)

Child 5–12 years 62.5 mg 4 times daily for 10–14 days (increased up to 250 mg 4 times daily if infection fails to respond or is life-threatening)

Child 12–18 years 125 mg 4 times daily for 10–14 days (increased up to 500 mg 4 times daily if infection fails to respond or is life-threatening)

CNS infection e.g. ventriculitis

• By intraventricular administration, seek specialist advice

Neonate 10 mg once every 24 hours

Child 1 month–18 years 10 mg once every 24 hours

Note for all children reduce to 5 mg daily if ventricular size reduced or increase to 15–20 mg once daily if ventricular size increased. Adjust dose according to CSF concentration after 3–4 days; aim for pre-dose ('trough') concentration less than 10 mg/litre. If CSF not draining freely reduce dose frequency to once every 2–3 days

Peritonitis associated with peritoneal dialysis

Add to each bag of dialysis fluid to achieve a concentration of 20–25 mg/litre

Eradication of methicillin-resistant *Staphylococcus aureus* from the respiratory tract in cystic fibrosis

• By inhalation of nebulised solution

Child 1 month–18 years 4 mg/kg (max. 250 mg) 2 or 4 times daily for 5 days

Note Vancomycin doses in BNFC for Children may differ from those in product literature

Administration Displacement value may be significant, consult product literature and local guidelines. For intermittent intravenous infusion, the reconstituted preparation should be further diluted in sodium chloride 0.9% or glucose 5% to a concentration of up

to 5 mg/mL; give over at least 60 minutes (rate not to exceed 10 mg/minute for doses over 500 mg); use continuous infusion only if intermittent not available (limited evidence); 10 mg/mL can be used if infused via a central venous line over at least 1 hour

Injection may be given orally; flavouring syrups may be added to the solution at the time of administration
For nebulisation administer required dose in 4 mL of sodium chloride 0.9% (or water for injections).

Safe Practice

For intraventricular administration, seek specialist advice

Vancomycin (Non-proprietary) (PoM)

Capsules, vancomycin (as hydrochloride) 125 mg, net price 28-cap pack = £132.47; 250 mg, 28-cap pack = £132.47. Label: 9

Injection, powder for reconstitution, vancomycin (as hydrochloride), for use as an infusion, net price 500-mg vial = £6.25; 1-g vial = £12.99

Note Can be used to prepare solution for oral administration

Vancocin® (Flynn) (PoM)

Matrigel capsules, vancomycin (as hydrochloride) 125 mg, net price 28-cap pack = £88.31. Label: 9

Injection, powder for reconstitution, vancomycin (as hydrochloride), for use as an infusion, net price 500-mg vial = £6.25; 1-g vial = £12.50

Note Can be used to prepare solution for oral administration

concentration can be used to optimise treatment in some patients (see Cautions). Pre-dose ('trough') concentration should be greater than 10 mg/litre (greater than 15–20 mg/litre in endocarditis) but less than 60 mg/litre

Indications and dose

Potentially serious Gram-positive infections including endocarditis, and serious infections due to *Staphylococcus aureus*

- By intravenous injection or intravenous infusion over 30 minutes

Neonate initially 16 mg/kg for one dose followed 24 hours later by 8 mg/kg once daily (intravenous infusion only)

Child 1 month–18 years initially 10 mg/kg (max. 400 mg) every 12 hours for 3 doses, then 6 mg/kg (max. 400 mg) once daily (after first 3 doses, subsequent doses can be given by intramuscular injection, if necessary, although intravenous route preferable); in severe infections (including burns, septicaemia, septic arthritis and osteomyelitis) initially 10 mg/kg every 12 hours for 3 doses then 10 mg/kg once daily

Administration For intermittent intravenous infusion, dilute reconstituted solution further in sodium chloride 0.9% or glucose 5%; give over 30 minutes. Intermittent intravenous infusion preferred in neonates

Targocid® (Sanofi-Aventis) (PoM)

Injection, powder for reconstitution, teicoplanin, net price 200-mg vial (with diluent) = £3.93; 400-mg vial (with diluent) = £7.32

Electrolytes Na^+ < 0.5 mmol/200- and 400-mg vial

TEICOPLANIN

Cautions vancomycin sensitivity; blood counts and liver and kidney function tests required—monitor renal and auditory function on prolonged administration during renal impairment or if other nephrotoxic or neurotoxic drugs given; monitor plasma-teicoplanin concentration if severe sepsis or burns, deep-seated staphylococcal infection (including bone and joint infection), endocarditis, renal impairment, and in intravenous drug abusers; **interactions:** Appendix 1 (teicoplanin)

Renal impairment use normal dose regimen on days 1–4, then use normal maintenance dose every 48 hours if estimated glomerular filtration rate 40–60 mL/minute/1.73 m² and use normal maintenance dose every 72 hours if estimated glomerular filtration rate less than 40 mL/minute/1.73 m²; see also Cautions above

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding no information available

Side-effects rash, pruritus; *less commonly* nausea, vomiting, diarrhoea, bronchospasm, dizziness, headache, fever, leucopenia, thrombocytopenia, eosinophilia, tinnitus, mild hearing loss, vestibular disorders, thrombophlebitis; *also reported* renal failure, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Pharmacokinetics plasma-teicoplanin concentration is not measured routinely because there is no clear relationship between plasma-teicoplanin concentration and toxicity. However, the plasma-teicoplanin

Linezolid

Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), and glycopeptide-resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is less than that recommended. Linezolid should be reserved for infections caused by Gram-positive bacteria when the organisms are resistant to other antibacterials or when patients cannot tolerate other antibacterials. Linezolid is **not** active against common Gram-negative organisms; it must be given in combination with other antibacterials for mixed infections that also involve Gram-negative organisms. There is limited information on use in children and expert advice should be sought. A higher incidence of blood disorders and optic neuropathy have been reported in patients receiving linezolid for more than the maximum recommended duration of 28 days.

LINEZOLID

Cautions monitor full blood count (including platelet count) weekly (see also Blood Disorders below); unless close observation and blood-pressure monitoring possible, avoid in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states; **interactions:** Appendix 1 (MAOIs)

Blood disorders

Haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) have been reported in patients receiving linezolid. It is recommended that full blood counts are monitored weekly. Close monitoring is recommended in patients who:

- receive treatment for more than 10–14 days;
- have pre-existing myelosuppression;
- are receiving drugs that may have adverse effects on haemoglobin, blood counts, or platelet function;
- have severe renal impairment.

If significant myelosuppression occurs, treatment should be stopped unless it is considered essential, in which case intensive monitoring of blood counts and appropriate management should be implemented.

CHM advice (optic neuropathy)

Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. The CHM recommends that:

- patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately;
- patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly, and referred to an ophthalmologist if necessary;
- visual function should be monitored regularly if treatment is required for longer than 28 days.

Monoamine oxidase inhibition Linezolid is a reversible, non-selective monoamine oxidase inhibitor (MAOI). Patients should avoid consuming large amounts of tyramine-rich foods (such as mature cheese, yeast extracts, undistilled alcoholic beverages, and fermented soya bean products). In addition, linezolid should not be given with another MAOI or within 2 weeks of stopping another MAOI. Unless close observation and blood-pressure monitoring is possible, avoid in those receiving SSRIs, 5HT₁ agonists ('triptans'), tricyclic antidepressants, sympathomimetics, dopaminergics, buspirone, pethidine and possibly other opioid analgesics. For other interactions see Appendix 1 (MAOIs)

Contra-indications see Monoamine Oxidase Inhibition above

Hepatic impairment no dose adjustment necessary but in severe hepatic impairment use only if potential benefit outweighs risk

Renal impairment no dose adjustment necessary but metabolites may accumulate if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; see also Blood Disorders above

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—present in milk in animal studies

Side-effects diarrhoea (antibiotic-associated colitis reported), nausea, vomiting, taste disturbances, headache; *less commonly* thirst, dry mouth, glossitis, stomatitis, tongue discoloration, abdominal pain, dyspepsia, gastritis, constipation, pancreatitis, hypertension, fever, fatigue, dizziness, insomnia, hypoaesthesia, paraesthesia, tinnitus, polyuria, leucopenia, thrombocytopenia, eosinophilia, electrolyte disturbances, blurred vision, rash, pruritus, diaphoresis, injection-site reactions; *rarely* tachycardia, transient ischaemic attacks, renal failure; also reported tooth discoloration, convulsions, lactic aci-

dosis, hyponatraemia, pancytopenia, anaemia, Stevens-Johnson syndrome, toxic epidermal necrolysis; peripheral and optic neuropathy reported on prolonged therapy (see also CHM Advice above)

Licensed use not licensed for use in children

Indications and dose

Pneumonia, complicated skin and soft-tissue infections caused by Gram-positive bacteria (initiated under expert supervision)

- By mouth or by intravenous infusion over 30–120 minutes

Neonate under 7 days 10 mg/kg every 12 hours, increase to every 8 hours if poor response

Neonate over 7 days 10 mg/kg every 8 hours

Child 1 month–12 years 10 mg/kg (max. 600 mg) every 8 hours

Child 12–18 years 600 mg every 12 hours

Zyvox® (Pharmacia) [PoM]

Tablets, f/c, linezolid 600 mg, net price 10-tab pack = £445.00. Label: 9, 10, patient information leaflet

Suspension, yellow, linezolid 100 mg/5 mL when reconstituted with water, net price 150 mL (orange-flavoured) = £222.50. Label: 9, 10 patient information leaflet

Excipients include aspartame 20 mg/5 mL (section 9.4.1)

Intravenous infusion, linezolid 2 mg/mL, net price 300-mL *Excel®* bag = £44.50

Excipients include Na⁺ 5 mmol/300-mL bag, glucose 13.71 g/300-mL bag

Polymyxins

The polymyxin antibiotic, **colistimethate sodium** (colistin sulfomethate sodium), is active against Gram-negative organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*. It is **not** absorbed by mouth and is given by injection for a systemic effect. Intravenous administration of colistimethate sodium should be reserved for Gram-negative infections resistant to other antibacterials; its major adverse effects are dose-related neurotoxicity and nephrotoxicity.

Colistimethate sodium is also given by inhalation as an adjunct to standard antibacterial therapy in patients with cystic fibrosis.

NICE guidance

Colistimethate sodium by dry powder inhalation for pseudomonal lung infection in cystic fibrosis (March 2013)

Colistimethate sodium dry powder for inhalation is recommended for chronic pulmonary infection caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis who would benefit from continued treatment, but do not tolerate the drug in its nebulised form. The manufacturer must provide colistimethate sodium dry powder for inhalation at the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS. Patients currently receiving colistimethate sodium dry powder for inhalation can continue treatment until they and their clinician consider it appropriate to stop.

www.nice.org.uk/TA276

Both colistimethate sodium and polymyxin B are included in some preparations for topical application.

COLISTIMETHATE SODIUM

(Colistin sulfomethate sodium)

Cautions acute porphyria (section 9.8.2); **interactions:** Appendix 1 (polymyxins)**Specific cautions for parenteral treatment** Monitor renal function**Specific cautions for inhaled treatment** Other inhaled drugs should be administered before colistimethate sodium. Measure lung function before and after initial dose of colistimethate sodium and monitor for bronchospasm; if bronchospasm occurs in a child not using a bronchodilator, repeat test using a bronchodilator before the dose of colistimethate sodium. Severe haemoptysis—risk of further haemorrhage**Contra-indications** myasthenia gravis**Renal impairment** reduce dose and monitor plasma-colistimethate sodium concentration during parenteral treatment—consult product literature**Pregnancy** clinical use suggests probably safe when used by inhalation; use parenteral treatment only if potential benefit outweighs risk**Breast-feeding** present in milk but poorly absorbed from gut; manufacturers advise avoid (or use only if potential benefit outweighs risk)**Side-effects****Specific side-effects for parenteral treatment**

Neurotoxicity reported especially with excessive doses (including apnoea, perioral and peripheral paraesthesia, vertigo, headache, muscle weakness; rarely vasomotor instability, slurred speech, confusion, psychosis, visual disturbances), nephrotoxicity; rash

Specific side-effects for inhaled treatment Sore throat, sore mouth, taste disturbances, nausea, vomiting, cough, bronchospasm, dysphonia; *less commonly* thirst, hypersalivation**Pharmacokinetics** plasma concentration monitoring recommended in renal impairment; recommended 'peak' plasma-colistimethate sodium concentration (approx. 1 hour after intravenous injection or infusion) 5–15 mg/litre; pre-dose ('trough') concentration 2–6 mg/litre**Licensed use** *Promixin*[®] powder for nebuliser solution not licensed for use in children under 2 years**Indications and dose*****Pseudomonas aeruginosa* infection in cystic fibrosis**

- By slow intravenous injection into a totally implantable venous access device, or by intravenous infusion (but see notes above)

Child 1 month–18 years**Body-weight under 60 kg** 25 000 units/kg every 8 hours**Body-weight over 60 kg** 2 million units every 8 hours

- By inhalation of nebulised solution

Child 1 month–2 years 0.5–1 million units twice daily; increased to 1 million units 3 times daily for subsequent respiratory isolates of *Ps. aeruginosa***Child 2–18 years** 1–2 million units twice daily; increased to 2 million units 3 times daily for subsequent respiratory isolates of *Ps. aeruginosa*

- By inhalation of powder

Child 6–18 years 1.66 million units twice daily**Administration** For intravenous infusion, dilute to a concentration of 40 000 units/mL with Sodium Chloride 0.9%; give over 30 minutes

For slow intravenous injection into a totally implantable venous access device, dilute to a concentration of

90 000 units/mL with Sodium Chloride 0.9% for child under 12 years (200 000 units/mL for child over 12 years)

For nebulisation administer required dose in 2–4 mL of sodium chloride 0.9% (or water for injections) or a 1:1 mixture of sodium chloride 0.9% and water for injection

Colistimethate sodium (Non-proprietary) (PoM)**Injection**, powder for reconstitution, colistimethate sodium, net price 1 million-unit vial = £1.68**Colomycin**[®] (Forest) (PoM)**Injection**, powder for reconstitution, colistimethate sodium, net price 1 million-unit vial = £1.80; 2 million-unit vial = £3.24**Electrolytes** (before reconstitution) $\text{Na}^+ < 0.5 \text{ mmol/l}$ million-unit and 2 million-unit vial**Note** *Colomycin*[®] Injection may be used for nebulisation**Promixin**[®] (Profile) (PoM)**Powder for nebuliser solution**, colistimethate sodium, net price 1 million-unit vial = £4.60.**Injection**, powder for reconstitution, colistimethate sodium, net price 1 million unit-vial = £2.30**Electrolytes** (before reconstitution) $\text{Na}^+ < 0.5 \text{ mmol/l}$ million-unit vial**Colobreathe**[®] (Forest) (PoM)**Dry powder for inhalation, hard capsule**, colistimethate sodium 1.66 million units/capsule, net price 56-cap pack (with *Turbospin*[®] inhaler device) = £968.80. Counselling, administration**Counselling** Rinse mouth with water after each dose**5.1.8 Sulfonamides and trimethoprim**

The importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic.

Sulfamethoxazole and trimethoprim are used in combination (as **co-trimoxazole**) because of their synergistic activity. However, co-trimoxazole is associated with rare but serious side-effects e.g. Stevens-Johnson syndrome and blood dyscrasias, notably bone marrow depression and agranulocytosis (see Restrictions on the Use of Co-trimoxazole below). Co-trimoxazole should be avoided in children less than 6 weeks of age (except for treatment and prophylaxis of *pneumocystis pneumonia*) because of the risk of kernicterus. There is a risk of haemolytic anaemia if used in children with glucose-6-phosphate dehydrogenase (G6PD) deficiency (section 9.1.5).**Restrictions on the use of co-trimoxazole**Co-trimoxazole is the drug of choice in the prophylaxis and treatment of *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia; it is also indicated for nocardiosis, *Stenotrophomonas maltophilia* infection [unlicensed indication], and toxoplasmosis. It should only be considered for use in infections of the urinary tract when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in acute otitis media in children when there is good reason to prefer it. Co-trimoxazole is also used for the treatment of infections caused by *Burkholderia cepacia* in cystic fibrosis [unlicensed indication].

Trimethoprim can be used alone for urinary- and respiratory-tract infections and for shigellosis and invasive salmonella infections. Trimethoprim has side-effects similar to co-trimoxazole but they are less severe and occur less frequently.

For *topical preparations* of sulfonamides used in the treatment of burns see section 13.10.1.1.

CO-TRIMOXAZOLE

A mixture of trimethoprim and sulfamethoxazole (sulfamethoxazole) in the proportions of 1 part to 5 parts

Cautions maintain adequate fluid intake; avoid in blood disorders (unless under specialist supervision); monitor blood counts on prolonged treatment; discontinue immediately if blood disorders or rash develop; predisposition to folate deficiency; asthma; G6PD deficiency (section 9.1.5); avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia); **interactions:** Appendix 1 (trimethoprim, sulfamethoxazole)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment manufacturer advises avoid in severe liver disease

Renal impairment use half normal dose if estimated glomerular filtration rate 15–30 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 15 mL/minute/1.73 m² and if plasma-sulfamethoxazole concentration cannot be monitored

Pregnancy teratogenic risk in first trimester (trimethoprim a folate antagonist). Neonatal haemolysis and methaemoglobinaemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded

Breast-feeding small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole)

Side-effects nausea, diarrhoea; headache, hyperkalaemia; rash (*very rarely* including Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity)—discontinue immediately; *less commonly* vomiting; *very rarely* glossitis, stomatitis, anorexia, liver damage (including jaundice and hepatic necrosis), pancreatitis, antibiotic-associated colitis, myocarditis, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, peripheral neuropathy, ataxia, tinnitus, vertigo, hallucinations, hypoglycaemia, blood disorders (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia), hyponatraemia, renal disorders including interstitial nephritis, arthralgia, myalgia, vasculitis, systemic lupus erythematosus, and uveitis; rhabdomyolysis reported in HIV-infected patients

Pharmacokinetics plasma concentration monitoring may be required with high doses or during moderate to severe renal impairment; seek expert advice

Licensed use not licensed for use in children under 6 weeks

Indications and dose

Treatment of susceptible infections (but see notes above) dose expressed as co-trimoxazole

• By mouth

Child 6 weeks–12 years 24 mg/kg twice daily

or

Child 6 weeks–6 months 120 mg twice daily

Child 6 months–6 years 240 mg twice daily

Child 6–12 years 480 mg twice daily

Child 12–18 years 960 mg twice daily

• By intravenous infusion

Child 6 weeks–18 years 18 mg/kg every 12 hours; increased in severe infection to 27 mg/kg (max. 1.44 g) every 12 hours

Treatment of *Pneumocystis jirovecii* (*P. carinii*) infections (undertaken where facilities for appropriate monitoring available—consult microbiologist and product literature)

• By mouth or by intravenous infusion

Child 1 month–18 years 60 mg/kg every 12 hours for 14–21 days; total daily dose may alternatively be given in 3–4 divided doses

Note oral route preferred

Prophylaxis of *Pneumocystis jirovecii* (*P. carinii*) infections

• By mouth

Child 1 month–18 years 450 mg/m² (max. 960 mg) twice daily for three days of the week (either consecutively or on alternate days)

Note dose regimens may vary, consult local guidelines

Note 480 mg of co-trimoxazole consists of sulfamethoxazole 400 mg and trimethoprim 80 mg

Administration for intermittent intravenous infusion may be further diluted in glucose 5% and 10% or sodium chloride 0.9%. Dilute contents of 1 ampoule (5 mL) to 125 mL, 2 ampoules (10 mL) to 250 mL or 3 ampoules (15 mL) to 500 mL; suggested duration of infusion 60–90 minutes (but may be adjusted according to fluid requirements); if fluid restriction necessary, 1 ampoule (5 mL) may be diluted with 75 mL glucose 5% and the required dose infused over max. 60 minutes; check container for haze or precipitant during administration. In severe fluid restriction may be given undiluted via a central venous line

Co-trimoxazole (Non-proprietary) (PoM)

Tablets, co-trimoxazole 480 mg, net price 28-tab pack = £3.74; 960 mg, 100 = £23.46. Label: 9

Brands include Fectrim[®], Fectrim[®] Forte

Paediatric oral suspension, co-trimoxazole 240 mg/5 mL, net price 100 mL = £1.12. Label: 9

Oral suspension, co-trimoxazole 480 mg/5 mL. Net price 100 mL = £4.41. Label: 9

Septin[®] (Aspen) (PoM)

Tablets, co-trimoxazole 480 mg, net price 100-tab pack = £15.52. Label: 9

Forte tablets, scored, co-trimoxazole 960 mg, net price 100-tab pack = £23.46. Label: 9

Adult suspension, co-trimoxazole 480 mg/5 mL, net price 100 mL (vanilla-flavoured) = £4.41. Label: 9

Paediatric suspension, sugar-free, co-trimoxazole 240 mg/5 mL. Net price 100 mL (banana- and vanilla-flavoured) = £2.45. Label: 9

Intravenous infusion, co-trimoxazole 96 mg/mL. To be diluted before use. Net price 5-mL amp = £1.78

Electrolytes Na⁺ 1.7 mmol/5 mL

Excipients include alcohol 13.2%, propylene glycol, sulfites

TRIMETHOPRIM

Cautions predisposition to folate deficiency; manufacturer recommends blood counts on long-term therapy (but evidence of practical value unsatisfactory); neonates (specialist supervision required); acute porphyria (section 9.8.2); **interactions:** Appendix 1 (trimethoprim)

Blood disorders On long-term treatment, patients and their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop

Contra-indications blood dyscrasias

Renal impairment use half normal dose after 3 days if estimated glomerular filtration rate 15–30 mL/minute/1.73 m²; use half normal dose if estimated glomerular filtration rate less than 15 mL/minute/1.73 m² (monitor plasma-trimethoprim concentration if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²)

Pregnancy teratogenic risk in first trimester (folate antagonist); manufacturers advise avoid

Breast-feeding present in milk—short-term use not known to be harmful

Side-effects gastro-intestinal disturbances including nausea and vomiting, pruritus, rashes, hyperkalaemia, depression of haematopoiesis; rarely erythema multiforme, toxic epidermal necrolysis, photosensitivity and other allergic reactions including angioedema and anaphylaxis; aseptic meningitis reported

Licensed use not licensed for use in children under 6 weeks

Indications and dose

Urinary-tract infections; respiratory-tract infections

- By mouth

Neonate initially 3 mg/kg as a single dose then 1–2 mg/kg twice daily

Child 1 month–12 years 4 mg/kg (max. 200 mg) twice daily

or

Child 6 weeks–6 months 25 mg twice daily

Child 6 months–6 years 50 mg twice daily

Child 6–12 years 100 mg twice daily

Child 12–18 years 200 mg twice daily

Prophylaxis of urinary-tract infection

Table 2, section 5.1

Pneumocystis pneumonia see p. 350

Trimethoprim (Non-proprietary) PoM

Tablets, trimethoprim 100 mg, net price 28 = £1.02; 200 mg, 14-tab pack = 90p. Label: 9

Brands include Trimopan®

Suspension, trimethoprim 50 mg/5 mL, net price 100 mL = £1.95. Label: 9

The regimens given below are recommended for the treatment of tuberculosis in the UK; variations occur in other countries. Either the unsupervised regimen or the supervised regimen described below should be used; the two regimens should **not** be used concurrently. Compliance with therapy is a major determinant of its success. Treatment needs to be carefully monitored in families in whom concordance may be problematic.

Initial phase The concurrent use of 4 drugs during the initial phase is designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug-resistant bacteria. The drugs are best given as combination preparations, provided the respective dose of each drug is appropriate, unless the child is unable to swallow the tablets or one of the components cannot be given because of resistance or intolerance. The treatment of choice for the initial phase is the daily use of isoniazid, rifampicin, pyrazinamide and ethambutol. However, care is needed in young children receiving ethambutol because of the difficulty in testing eyesight and in obtaining reports of visual symptoms (see below). Treatment should be started without waiting for culture results if clinical features or histology results are consistent with tuberculosis; treatment should be continued even if initial culture results are negative. The initial phase drugs should be continued for 2 months. Where a positive culture for *M. tuberculosis* has been obtained, but susceptibility results are not available after 2 months, treatment with rifampicin, isoniazid, pyrazinamide and ethambutol should be continued until full susceptibility is confirmed, even if this is for longer than 2 months.

Streptomycin is rarely used in the UK although it may be used in the initial phase of treatment if resistance to isoniazid has been established before therapy is commenced and ethambutol is contra-indicated.

Continuation phase After the initial phase, treatment is continued for a further 4 months with isoniazid and rifampicin (preferably given as a combination preparation). Longer treatment is necessary for meningitis, direct spinal cord involvement, and for resistant organisms which may also require modification of the regimen.

Unsupervised treatment The following regimen should be used for those who are likely to take antituberculous drugs reliably **without supervision** by a healthcare worker. Children and families who are unlikely to comply with daily administration of antituber-

5.1.9 Antituberculosis drugs

Tuberculosis is treated in two phases—an *initial phase* using 4 drugs and a *continuation phase* using two drugs in fully sensitive cases. Treatment requires specialised knowledge, particularly where the disease involves resistant organisms or non-respiratory organs.

culous drugs should be treated with the regimen described under Supervised Treatment.

Recommended dosage for standard unsupervised 6-month treatment

Isoniazid (for 6 months)	Child 1 month–18 years 10 mg/kg (max. 300 mg) once daily
Rifampicin (for 6 months)	Child 1 month–18 years 15 mg/kg once daily (max. 450 mg daily if body-weight under 50 kg; max. 600 mg daily if body-weight 50 kg and over)
Pyrazinamide (for 2-month initial phase only)	Child 1 month–18 years 35 mg/kg once daily (max. 1.5 g daily if body-weight under 50 kg; max. 2 g daily if body-weight 50 kg and over)
Ethambutol (for 2-month initial phase only)	Child 1 month–18 years 20 mg/kg once daily

Note In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. The exception is ethambutol due to the risk of toxicity. Doses may also need to be recalculated to allow for weight gain in younger children. The fixed-dose combination preparations (*Rifater*®, *Rifinah*®) are unlicensed for use in children. Consideration may be given to use of these preparations in older children, provided the respective dose of each drug is appropriate for the weight of the child.

Pregnancy The standard regimen (above) may be used during pregnancy. Streptomycin should not be given in pregnancy.

Breast-feeding The standard regimen (above) may be used during breast-feeding.

Neonates Congenital tuberculosis is acquired from maternal extrapulmonary sites at birth, particularly the genital tract; if infection is suspected, the baby will require treatment with isoniazid 10 mg/kg once daily, rifampicin 15 mg/kg once daily, pyrazinamide 35 mg/kg once daily, and ethambutol 20 mg/kg once daily. Isoniazid, rifampicin, pyrazinamide, and ethambutol are used for 2 months during the initial phase of treatment. After the initial phase, treatment is continued for a further 4 months with isoniazid and rifampicin.

Supervised treatment Drug administration needs to be **fully supervised** by a healthcare worker (directly observed therapy, DOT) in children or families who cannot comply reliably with the treatment regimen. These patients are given isoniazid, rifampicin, pyrazinamide and ethambutol (or streptomycin) 3 times a week under supervision for the first 2 months followed by

isoniazid and rifampicin 3 times a week for a further 4 months.

Recommended dosage for intermittent supervised 6-month treatment

Isoniazid (for 6 months)	Child 1 month–18 years 15 mg/kg (max. 900 mg) 3 times a week
Rifampicin (for 6 months)	Child 1 month–18 years 15 mg/kg (max. 900 mg) 3 times a week
Pyrazinamide (for 2-month initial phase only)	Child 1 month–18 years 50 mg/kg 3 times a week (max. 2 g 3 times a week if body-weight under 50 kg; max. 2.5 g 3 times a week if body-weight 50 kg and over)
Ethambutol (for 2-month initial phase only)	Child 1 month–18 years 30 mg/kg 3 times a week

Note In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. The exception is ethambutol due to the risk of toxicity. Doses may also need to be recalculated to allow for weight gain in younger children. The fixed-dose combination preparations (*Rifater*®, *Rifinah*®) are unlicensed for use in children. Consideration may be given to use of these preparations in older children, provided the respective dose of each drug is appropriate for the weight of the child.

Immunocompromised patients Multi-resistant *Mycobacterium tuberculosis* may be present in immunocompromised children. The organism should always be cultured to confirm its type and drug sensitivity. Confirmed *M. tuberculosis* infection sensitive to first-line drugs should be treated with a standard 6-month regimen; after completing treatment, children should be closely monitored. The regimen may need to be modified if infection is caused by resistant organisms, and specialist advice is needed.

Specialist advice should be sought about tuberculosis treatment or chemoprophylaxis in a HIV-positive individual; care is required in choosing the regimen and in avoiding potentially serious interactions. Starting antiretroviral treatment in the first 2 months of anti-tuberculosis treatment increases the risk of immune reconstitution syndrome.

Infection may also be caused by other mycobacteria e.g. *M. avium* complex in which case specialist advice on management is needed.

Corticosteroids A corticosteroid should be given (in addition to antituberculosis therapy) for meningeal or pericardial tuberculosis.

Prevention of tuberculosis Chemoprophylaxis may be required in children who are close contacts of a case of smear-positive pulmonary tuberculosis and who are severely immunosuppressed (including congenital immunodeficiencies, cytotoxic or immunosuppressive therapy) and in those who have evidence of latent tuberculosis and require treatment with immunosuppressants; expert advice should be sought.

Chemoprophylaxis involves use of either isoniazid alone for 6 months or of isoniazid and rifampicin for 3 months (see Table 2, section 5.1).

For prevention of tuberculosis in susceptible close contacts or those who have become tuberculin-positive, see Table 2, section 5.1. For advice on immunisation against tuberculosis and tuberculin testing, see section 14.4.

Monitoring Since isoniazid, rifampicin and pyrazinamide are associated with liver toxicity, *hepatic function* should be checked before treatment with these drugs. Those with pre-existing liver disease should have frequent checks particularly in the first 2 months. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. In view of the need to comply fully with antituberculous treatment on the one hand and to guard against serious liver damage on the other, children and their carers should be informed carefully how to recognise signs of liver disorders and advised to discontinue treatment and seek **immediate** medical attention should symptoms of liver disease occur.

Renal function should be checked before treatment with antituberculous drugs and appropriate dosage adjustments made. Streptomycin or ethambutol should preferably be avoided in patients with renal impairment, but if used, the dose should be reduced and the plasma-drug concentration monitored.

Visual acuity should be tested before ethambutol is used (see below).

Major causes of treatment failure are incorrect prescribing by the physician and inadequate compliance by the child or their carer. Monthly tablet counts and urine examination (rifampicin imparts an orange-red coloration) may be useful indicators of compliance with treatment. Avoid both excessive and inadequate dosage. Treatment should be supervised by a specialist paediatrician.

Isoniazid is cheap and highly effective. Like rifampicin it should always be included in any antituberculous regimen unless there is a specific contra-indication. Its only common side-effect is peripheral neuropathy which is more likely to occur where there are pre-existing risk factors such as diabetes, chronic renal failure, pregnancy, malnutrition and HIV infection. In these circumstances pyridoxine (section 9.6.2) should be given prophylactically from the start of treatment. Other side-effects such as hepatitis (important: see Monitoring above) and psychosis are rare.

Rifampicin, a rifamycin, is a key component of any antituberculous regimen. Like isoniazid it should always be included unless there is a specific contra-indication. During the first two months ('initial phase') of rifampicin administration transient disturbance of liver function with elevated serum transaminases is common but generally does not require interruption of treatment. Occasionally more serious liver toxicity requires a change of treatment particularly in those with pre-existing liver disease (important: see Monitoring above).

On intermittent treatment six toxicity syndromes have been recognised—influenza-like, abdominal, and respiratory symptoms, shock, renal failure, and thrombocytopenic purpura—and can occur in 20 to 30% of patients.

Rifampicin induces hepatic enzymes which accelerate the metabolism of several drugs including oestrogens, corticosteroids, phenytoin, sulfonylureas, and antico-

agulants; **interactions:** Appendix 1 (rifamycins). **Important:** the effectiveness of hormonal contraceptives is reduced and alternative family planning advice should be offered (section 7.3.1).

Rifabutin is indicated in adults for *prophylaxis* against *M. avium* complex infections in patients with a low CD4 count; it is also licensed in adults for the *treatment* of non-tuberculous mycobacterial disease and pulmonary tuberculosis. There is limited experience in children. As with rifampicin it induces hepatic enzymes and the effectiveness of hormonal contraceptives is reduced requiring alternative family planning methods.

Pyrazinamide is a bactericidal drug only active against intracellular dividing forms of *Mycobacterium tuberculosis*; it exerts its main effect only in the first two or three months. It is particularly useful in tuberculous meningitis because of good meningeal penetration. It is not active against *M. bovis*. Serious liver toxicity may occasionally occur (important: see Monitoring above).

Ethambutol is included in a treatment regimen if isoniazid resistance is suspected; it can be omitted if the risk of resistance is low.

Side-effects of ethambutol are largely confined to visual disturbances in the form of loss of acuity, colour blindness, and restriction of visual fields. These toxic effects are more common where excessive dosage is used or if the child's renal function is impaired. The earliest features of ocular toxicity are subjective and children and their carers should be advised to discontinue therapy immediately if deterioration in vision develops and promptly seek further advice. Early discontinuation of the drug is almost always followed by recovery of eyesight. Those who cannot understand warnings about visual side-effects should, if possible, be given an alternative drug. In particular, ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately.

Where possible visual acuity should be tested by Snellen chart before treatment with ethambutol.

Streptomycin is now rarely used in the UK except for resistant organisms. Plasma-drug concentration should be measured in patients with impaired renal function in whom streptomycin must be used with great care.

Drug-resistant tuberculosis should be treated by a specialist paediatrician with experience in such cases, and where appropriate facilities for infection-control exist. Second-line drugs available for infections caused by resistant organisms, or when first-line drugs cause unacceptable side-effects, include amikacin, capreomycin, cycloserine, newer macrolides (e.g. azithromycin and clarithromycin), quinolones (e.g. moxifloxacin) and prothionamide (prothionamide; no longer on UK market). Availability of suitable formulations may limit choice in children.

CYCLOSERINE

Cautions monitor haematological, renal, and hepatic function; **interactions:** Appendix 1 (cycloserine)

Contra-indications epilepsy, depression, severe anxiety, psychotic states, alcohol dependence

Renal impairment increase interval between doses if creatinine clearance less than 50 mL/minute/1.73 m² and monitor blood-cycloserine concentration

Pregnancy manufacturer advises use only if potential benefit outweighs risk—crosses the placenta

Breast-feeding present in milk—amount too small to be harmful

Side-effects mainly neurological, including headache, dizziness, vertigo, drowsiness, tremor, convulsions, confusion, psychosis, depression (discontinue or reduce dose if symptoms of CNS toxicity); rashes, allergic dermatitis (discontinue or reduce dose); megaloblastic anaemia; changes in liver function tests; heart failure at high doses reported

Pharmacokinetics blood concentration should not exceed a peak concentration of 30 mg/litre (measured 3–4 hours after the dose); penetrates CNS

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Tuberculosis resistant to first-line drugs, used in combination with other drugs

• By mouth

Child 2–12 years initially 5 mg/kg (max. 250 mg) twice daily, adjusted according to blood concentration and response up to 10 mg/kg (max. 500 mg) twice daily

Child 12–18 years initially 250 mg twice daily for 2 weeks adjusted according to blood concentration and response to max. 500 mg twice daily

Cycloserine (King) (PoM)

Capsules, red/grey cycloserine 250 mg, net price 100-cap pack = £402.63. Label: 2, 8

ETHAMBUTOL HYDROCHLORIDE

Cautions test visual acuity before treatment and warn patients to report visual changes—see notes above; young children (see notes above)—routine ophthalmological monitoring recommended

Contra-indications optic neuritis, poor vision

Renal impairment if creatinine clearance less than 30 mL/minute/1.73 m², use 15–25 mg/kg (max. 2.5 g) 3 times a week and monitor plasma-ethambutol concentration; risk of optic nerve damage

Pregnancy not known to be harmful; see also p. 295

Breast-feeding amount too small to be harmful; see also p. 295

Side-effects optic neuritis, red/green colour blindness, peripheral neuritis, rarely rash, pruritus, urticaria, thrombocytopenia

Pharmacokinetics 'peak' concentration (2–2.5 hours after dose) should be 2–6 mg/litre (7–22 micromol/litre); 'trough' (pre-dose) concentration should be less than 1 mg/litre (4 micromol/litre)

Indications and dose

Tuberculosis, used in combination with other drugs see notes above

Ethambutol (Non-proprietary) (PoM)

Tablets, ethambutol hydrochloride 100 mg, net price 56-tab pack = £11.52; 400 mg, 56-tab pack = £42.74. Label: 8

ISONIAZID

Cautions see Monitoring in notes above; also slow acetylator status (increased risk of side-effects); epilepsy; history of psychosis; alcohol dependence, malnutrition, diabetes mellitus, HIV infection (risk of

peripheral neuritis); acute porphyria (section 9.8.2); **interactions:** Appendix 1 (isoniazid)

Hepatic disorders Children and their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

Contra-indications drug-induced liver disease

Hepatic impairment use with caution; monitor liver function regularly and particularly frequently in the first 2 months; see also Hepatic Disorders above

Renal impairment risk of ototoxicity and peripheral neuropathy; prophylactic pyridoxine recommended

Pregnancy not known to be harmful; prophylactic pyridoxine recommended; see also p. 295

Breast-feeding monitor infant for possible toxicity; theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother; see also p. 295

Side-effects nausea, vomiting, constipation, dry mouth; peripheral neuritis with high doses (pyridoxine prophylaxis, see notes above), optic neuritis, convulsions, psychotic episodes, vertigo; hypersensitivity reactions including fever, Stevens-Johnson syndrome, purpura; blood disorders including agranulocytosis, haemolytic anaemia, aplastic anaemia; hepatitis; pancreatitis; interstitial pneumonitis; systemic lupus erythematosus-like syndrome, pella-gra, hyperreflexia, difficulty with micturition, hyperglycaemia, and gynaecomastia reported; hearing loss and tinnitus (in children with end-stage renal impairment); when used with tyramine or histamine rich foods, tachycardia, palpitation, hypotension, flushing, headache, dizziness, and sweating also reported

Indications and dose

Tuberculosis, used in combination with other drugs see notes above

Isoniazid (Non-proprietary) (PoM)

Tablets, isoniazid 50 mg, net price 56-tab pack = £13.75; 100 mg, 28-tab pack = £13.75. Label: 8, 22

Injection, isoniazid 25 mg/mL, net price 2-mL amp = £24.11

PYRAZINAMIDE

Cautions see Monitoring in notes above; also diabetes; **interactions:** Appendix 1 (pyrazinamide)

Hepatic disorders Children and their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

Hepatic impairment monitor hepatic function—idiosyncratic hepatotoxicity more common; avoid in severe hepatic impairment; see also Hepatic Disorders above

Renal impairment if estimated glomerular filtration rate less than 30 mL/minute/1.73 m², use 25–30 mg/kg 3 times a week

Pregnancy manufacturer advises use only if potential benefit outweighs risk; see also p. 295

Breast-feeding amount too small to be harmful; see also p. 295

Side-effects hepatotoxicity including fever, anorexia, hepatomegaly, splenomegaly, jaundice, liver failure; nausea, vomiting, dysuria, arthralgia, sideroblastic anaemia, thrombocytopenia, rash and occasionally photosensitivity

Indications and dose

Tuberculosis in combination with other drugs see notes above

Zinamide® (Genus)

Tablets, scored, pyrazinamide 500 mg, net price 30-tab pack = £31.35. Label: 8

RIFABUTIN

Cautions see under Rifampicin; acute porphyria (section 9.8.2)

Contra-indications rifamycin hypersensitivity

Hepatic impairment reduce dose in severe impairment

Renal impairment use half normal dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, pyrexia, blood disorders (including leucopenia, anaemia, thrombocytopenia, and rarely haemolysis), myalgia, rash; *less commonly* vomiting, raised liver enzymes, jaundice, arthralgia, corneal deposits, uveitis especially following high doses or concomitant use with drugs that increase plasma concentration—see also **interactions**: Appendix 1 (rifamycins), hypersensitivity reactions (including eosinophilia, bronchospasm), skin, urine, saliva and other body secretions coloured orange-red; *also reported* hepatitis, influenza-like symptoms, chest pain, dyspnoea

Licensed use not licensed for use in children

Indications and dose

Prophylaxis of *Mycobacterium avium* complex infections in immunosuppressed patients with low CD4 count (see product literature) Also see notes above

• By mouth

Child 1–12 years 5 mg/kg (max. 300 mg) once daily

Child 12–18 years 300 mg once daily

Treatment of non-tuberculous mycobacterial disease, in combination with other drugs

• By mouth

Child 1 month–12 years 5 mg/kg once daily for up to 6 months after cultures negative

Child 12–18 years 450–600 mg once daily for up to 6 months after cultures negative

Treatment of pulmonary tuberculosis, in combination with other drugs

• By mouth

Child 12–18 years 150–450 mg once daily for at least 6 months

Mycobutin® (Pharmacia) (PoM)

Capsules, red-brown, rifabutin 150 mg. Net price 30-cap pack = £90.38. Label: 8, 14, counselling, lenses, see under Rifampicin

RIFAMPICIN

Cautions see Monitoring in notes above; also liver function tests and blood counts in hepatic disorders, and on prolonged therapy, see also below; **important**:

effectiveness of hormonal contraceptives is reduced and alternative family planning advice should be offered (see also section 7.3.1); discolours soft contact lenses; see also notes above; **interactions**: Appendix 1 (rifamycins)

Note If treatment interrupted re-introduce with low dosage and increase gradually; discontinue permanently if serious side-effects develop

Hepatic disorders Children and their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

Contra-indications jaundice; rifamycin hypersensitivity; acute porphyria (section 9.8.2)

Hepatic impairment impaired elimination; monitor liver function; avoid or do not exceed 8 mg/kg daily; see also Cautions above

Renal impairment use with caution if dose above 10 mg/kg daily

Pregnancy manufacturers advise very high doses teratogenic in *animal* studies in first trimester; risk of neonatal bleeding may be increased in third trimester; see also p. 295

Breast-feeding amount too small to be harmful; see also p. 295

Side-effects gastro-intestinal symptoms including anorexia, nausea, vomiting, diarrhoea (antibiotic-associated colitis reported); headache, drowsiness; those occurring mainly on intermittent therapy include influenza-like symptoms (with chills, fever, dizziness, bone pain), respiratory symptoms (including shortness of breath), collapse and shock, haemolytic anaemia, disseminated intravascular coagulation and acute renal failure, thrombocytopenic purpura; alterations of liver function, jaundice; flushing, urticaria, and rashes; other side-effects reported include oedema, psychoses, adrenal insufficiency, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigoid reactions, leucopenia, eosinophilia, menstrual disturbances; urine, saliva, and other body secretions coloured orange-red; thrombophlebitis reported if infusion used for prolonged period

Licensed use not licensed for use in children for pruritus due to cholestasis

Indications and dose

Tuberculosis, in combination with other drugs see notes above

Prophylaxis of meningococcal meningitis Table 2, section 5.1

Prophylaxis of *Haemophilus influenzae* type b disease Table 2, section 5.1

Brucellosis, legionnaires disease, serious staphylococcal infections, in combination with other antibacterials

• By mouth or by intravenous infusion

Neonates 5–10 mg/kg twice daily

Child 1 month–1 year 5–10 mg/kg twice daily

Child 1–18 years 10 mg/kg (max. 600 mg) twice daily

Pruritus due to cholestasis

• By mouth

Child 1 month–18 years 5–10 mg/kg (max. 600 mg) once daily

Administration Displacement value may be significant, consult local reconstitution guidelines; reconstitute with solvent provided. May be further diluted with glucose 5% or sodium chloride 0.9% to a final concentration of 1.2 mg/mL. Infuse over 2–3 hours.

Rifampicin (Non-proprietary) PoM

Capsules, rifampicin 150 mg, net price 100 = £14.04; 300 mg, 100 = £44.80. Label: 8, 14, 22, counselling, see contact lenses above

Rifadin[®] (Sanofi-Aventis) PoM

Capsules, rifampicin 150 mg (blue/red), net price 100-cap pack = £18.32; 300 mg (red), 100-cap pack = £36.63. Label: 8, 14, 22, counselling, see contact lenses above

Syrup, red, rifampicin 100 mg/5 mL (raspberry-flavoured). Net price 120 mL = £3.56. Label: 8, 14, 22, counselling, see contact lenses above

Excipients include sucrose

Intravenous infusion, powder for reconstitution, rifampicin. Net price 600-mg vial (with solvent) = £7.67

Electrolytes $\text{Na}^+ < 0.5 \text{ mmol/l vial}$

Rimactane[®] (Sandoz) PoM

Capsules, rifampicin 150 mg (red), net price 60-cap pack = £15.83; 300 mg (red/brown), 60-cap pack = £25.92. Label: 8, 14, 22, counselling, see contact lenses above

Combined preparations

See notes above

Rifater[®] (Sanofi-Aventis) PoM

Tablets, pink, s/c, rifampicin 120 mg, isoniazid 50 mg, pyrazinamide 300 mg. Net price 100-tab pack = £21.95. Label: 8, 14, 22, counselling, see contact lenses above

Rifinah[®] 150/100 (Sanofi-Aventis) PoM

Tablets, pink, s/c, rifampicin 150 mg, isoniazid 100 mg, net price 84-tab pack = £15.91. Label: 8, 14, 22, counselling, see contact lenses above

Rifinah[®] 300/150 (Sanofi-Aventis) PoM

Tablets, orange, s/c, rifampicin 300 mg, isoniazid 150 mg, net price 56-tab pack = £26.24. Label: 8, 14, 22, counselling, see contact lenses above

Note Some stock packaged as *Rifinah 150/300*

STREPTOMYCIN

Cautions see under Aminoglycosides, section 5.1.4; measure plasma-concentration in renal impairment; **interactions:** Appendix 1 (aminoglycosides)

Contra-indications see under Aminoglycosides, section 5.1.4

Renal impairment see under Aminoglycosides, section 5.1.4

Pregnancy see under Aminoglycosides, section 5.1.4

Side-effects see under Aminoglycosides, section 5.1.4; also hypersensitivity reactions, paraesthesia of mouth

Pharmacokinetics one-hour ('peak') concentration should be 15–40 mg/litre; pre-dose ('trough') concentration should be less than 5 mg/litre (less than 1 mg/litre in renal impairment)

Licensed use not licensed for use in children

Indications and dose

Tuberculosis, resistant to other treatment, in combination with other drugs

• By deep intramuscular injection

Child 1 month–18 years 15 mg/kg (max. 1 g) once daily

Adjunct to doxycycline in brucellosis, expert advice essential

• By deep intramuscular injection

Child 1 month–18 years 5–10 mg/kg every 6 hours; total daily dose may alternatively be given in 2–3 divided doses

Important Side-effects increase after a cumulative dose of 100 g, which should only be exceeded in exceptional circumstances

Streptomycin Sulfate (Non-proprietary) PoM

Injection, powder for reconstitution, streptomycin (as sulfate), net price 1-g vial = £15.00

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

5.1.10 Antileprotic drugs

Classification not used in *BNF for Children*.

5.1.11 Metronidazole

Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa. It is also used for surgical and gynaecological sepsis in which its activity against colonic anaerobes, especially *Bacteroides fragilis*, is important. Metronidazole by mouth is effective for the treatment of *Clostridium difficile* infection (see also section 1.5); it can be given by intravenous infusion if oral treatment is inappropriate. Metronidazole is well absorbed orally and the intravenous route is normally reserved for severe infections. Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible. Intravenous metronidazole is used for the treatment of established cases of tetanus; diazepam (section 10.2.2) and tetanus immunoglobulin (section 14.5.2) are also used.

Topical metronidazole (section 13.10.1.2) reduces the odour produced by anaerobic bacteria in fungating tumours; it is also used in the management of rosacea (section 13.6).

Oral infections Metronidazole is an alternative to a penicillin for the treatment of many oral infections where the patient is allergic to penicillin or the infection is due to beta-lactamase-producing anaerobes (Table 1, section 5.1). It is the drug of first choice for the treatment of acute necrotising ulcerative gingivitis (Vincent's infection) and pericoronitis; amoxicillin is a suitable alternative (section 5.1.1.3). For these purposes treatment with metronidazole for 3 days is sufficient, but the duration of treatment may need to be longer in pericoronitis. Tinidazole is licensed for the treatment of acute ulcerative gingivitis.

METRONIDAZOLE

Cautions disulfiram-like reaction with alcohol, clinical and laboratory monitoring advised if treatment exceeds 10 days; **interactions:** Appendix 1 (metronidazole)

Hepatic impairment in severe liver disease reduce total daily dose to one-third, and give once daily; use with caution in hepatic encephalopathy

Pregnancy manufacturer advises avoidance of high-dose regimens; use only if potential benefit outweighs risk

Breast-feeding significant amount in milk; manufacturer advises avoid large single doses though otherwise compatible; may give milk a bitter taste

Side-effects gastro-intestinal disturbances (including nausea and vomiting), taste disturbances, furred tongue, oral mucositis, anorexia; *very rarely* hepatitis, jaundice, pancreatitis, drowsiness, dizziness, headache, ataxia, psychotic disorders, darkening of urine, thrombocytopenia, pancytopenia, myalgia, arthralgia, visual disturbances, rash, pruritus, and erythema multiforme; on prolonged or intensive therapy peripheral neuropathy, transient epileptiform seizures, and leucopenia; also reported aseptic meningitis, optic neuropathy

Indications and dose

Protozoal infections section 5.4.2

Anaerobic infections (usually treated for 7 days and for 10–14 days in *Clostridium difficile* infection)

• By mouth

Child 1–2 months 7.5 mg/kg every 12 hours

Child 2 months–12 years 7.5 mg/kg (max. 400 mg) every 8 hours

Child 12–18 years 400 mg every 8 hours

• By rectum

Child 1 month–1 year 125 mg 3 times daily for 3 days, then twice daily thereafter

Child 1–5 years 250 mg 3 times daily for 3 days, then twice daily thereafter

Child 5–10 years 500 mg 3 times daily, for 3 days, then twice daily thereafter

Child 10–18 years 1 g 3 times daily for 3 days, then twice daily thereafter

• By intravenous infusion over 20–30 minutes

Neonate less than 26 weeks corrected gestational age 15 mg/kg as a single loading dose followed after 24 hours by 7.5 mg/kg daily

Neonate 26–34 weeks corrected gestational age 15 mg/kg as a single loading dose followed after 12 hours by 7.5 mg/kg every 12 hours

Neonate over 34 weeks corrected gestational age 15 mg/kg as a single loading dose followed after 8 hours by 7.5 mg/kg every 8 hours

Child 1–2 months 15 mg/kg as a single loading dose followed after 8 hours by 7.5 mg/kg every 8 hours

Child 2 months–18 years 7.5 mg/kg (max. 500 mg) every 8 hours

Pelvic inflammatory disease (see also Table 1, section 5.1)

• By mouth

Child 12–18 years 400 mg twice daily for 14 days

Acute ulcerative gingivitis and other acute dental infections

• By mouth

Child 1–3 years 50 mg every 8 hours

Child 3–7 years 100 mg every 12 hours

Child 7–10 years 100 mg every 8 hours

Child 10–18 years 200–250 mg every 8 hours

***Helicobacter pylori* eradication** section 1.3

Fistulating Crohn's disease section 1.5

Surgical prophylaxis

• By mouth

Child 1 month–12 years 30 mg/kg (max. 500 mg) 2 hours before the procedure

Child 12–18 years 400–500 mg 2 hours before the procedure; up to 3 further doses of 400–500 mg may be given every 8 hours for high-risk procedures

• By intravenous infusion

Neonate under 40 weeks corrected gestational age 10 mg/kg up to 30 minutes before the procedure

Neonate over 40 weeks corrected gestational age 20–30 mg/kg up to 30 minutes before the procedure

Child 1 month–12 years 30 mg/kg (max. 500 mg) up to 30 minutes before the procedure

Child 12–18 years 500 mg up to 30 minutes before the procedure; up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures

• By rectum

Child 5–10 years 500 mg 2 hours before surgery; up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures

Child 10–18 years 1 g 2 hours before surgery; up to 3 further doses of 1 g may be given every 8 hours for high-risk procedures

Metronidazole (Non-proprietary) (PoM)

Tablets, metronidazole 200 mg, net price 21-tab pack = £1.13; 400 mg, 21-tab pack = £1.21. Label: 4, 9, 21, 25, 27

Brands include *Vaginyl*®

Dental prescribing on NHS Metronidazole Tablets may be prescribed

Tablets, metronidazole 500 mg, net price 21-tab pack = £35.75. Label: 4, 9, 21, 25, 27

Dental prescribing on NHS Metronidazole Tablets may be prescribed

Suspension, metronidazole (as benzoate) 200 mg/5 mL. Net price 100 mL = £29.33. Label: 4, 9

Brands include *Norzol*®

Dental prescribing on NHS Metronidazole Oral Suspension may be prescribed

Intravenous infusion, metronidazole 5 mg/mL. Net price 20-mL amp = £1.56, 100-mL container = £3.10

Flagyl® (Winthrop) (PoM)

Tablets, both f/c, ivory, metronidazole 200 mg, net price 21-tab pack = £4.49; 400 mg, 14-tab pack = £6.34. Label: 4, 9, 21, 25, 27

Suppositories, metronidazole 500 mg, net price 10 = £15.18; 1 g, 10 = £23.06. Label: 4, 9

Metrolyl® (Sandoz) (PoM)

Intravenous infusion, metronidazole 5 mg/mL, net price 100-mL Steriflex® bag = £1.22

Electrolytes Na⁺ 14.53 mmol/100-mL bag

Suppositories, metronidazole 500 mg, net price 10 = £12.34; 1 g, 10 = £18.34. Label: 4, 9

5.1.12 Quinolones

Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, campylobacter, neisseria, and pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as *Streptococcus pneumoniae* and *Enterococcus faecalis*; it should not be used for pneumococcal pneumonia. It is active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin is licensed in children over 1 year of age for pseudomonal infections in cystic fibrosis, for complicated urinary-tract infections (section 5.1.13), and for treatment and prophylaxis of inhalation anthrax. When the benefits of treatment outweigh the risks, ciprofloxacin is licensed in children over 1 year of age for severe infections of the respiratory tract and of the gastro-intestinal system (including typhoid fever). It is also used in the treatment of septicæmia caused by multi-resistant organisms (usually hospital acquired) and gonorrhoea (although resistance is increasing). Ciprofloxacin is also used in the prophylaxis of meningococcal disease.

Nalidixic acid may be used in uncomplicated urinary-tract infections that are resistant to other antibiotics (section 5.1.13).

Many staphylococci are resistant to quinolones and their use should be avoided in MRSA infections.

Ofloxacin eye drops are used in ophthalmic infections (section 11.3.1).

There is much less experience of the other quinolones in children; expert advice should be sought.

Anthrax *Inhalation* or *gastro-intestinal anthrax* should be treated initially with either **ciprofloxacin** or, in children over 12 years, **doxycycline** [unlicensed indication] (section 5.1.3) combined with one or two other antibacterials (such as amoxicillin, benzylpenicillin, chloramphenicol, clarithromycin, clindamycin, imipenem with cilastatin, rifampicin [unlicensed indication], and vancomycin). When the condition improves and the sensitivity of the *Bacillus anthracis* strain is known, treatment may be switched to a single antibacterial. Treatment should continue for 60 days because germination may be delayed.

Cutaneous anthrax should be treated with either ciprofloxacin [unlicensed indication] or doxycycline [unlicensed indication] (section 5.1.3) for 7 days. Treatment may be switched to amoxicillin (section 5.1.1.3) if the infecting strain is susceptible. Treatment may need to be extended to 60 days if exposure is due to aerosol. A combination of antibacterials for 14 days is recommended for cutaneous anthrax with systemic features, extensive oedema, or lesions of the head or neck.

Ciprofloxacin or doxycycline may be given for *post-exposure prophylaxis*. If exposure is confirmed, antibacterial prophylaxis should continue for 60 days. Antibacterial prophylaxis may be switched to amoxicillin

after 10–14 days if the strain of *B. anthracis* is susceptible. Vaccination against anthrax (section 14.4) may allow the duration of antibacterial prophylaxis to be shortened.

Cautions Quinolones should be used with caution in children with a history of epilepsy or conditions that predispose to seizures, in G6PD deficiency (section 9.1.5), myasthenia gravis (risk of exacerbation). Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs). Quinolones can prolong the QT interval. Ciprofloxacin and nalidixic acid should be used with caution in children with risk factors for QT interval prolongation (e.g. electrolyte disturbances, acute myocardial infarction, heart failure with reduced left ventricular ejection fraction, bradycardia, congenital long QT syndrome, concomitant use with other drugs known to prolong the QT interval, history of symptomatic arrhythmias). The CSM has warned that quinolones may induce **convulsions** in patients with or without a history of convulsions; taking NSAIDs at the same time may also induce them. Other **interactions**: Appendix 1 (quinolones).

Quinolones cause arthropathy in the weight-bearing joints of immature *animals* and are therefore generally not recommended in children and growing adolescents. However, the significance of this effect in humans is uncertain and in some specific circumstances short-term use of a quinolone in children is justified. Nalidixic acid is used for resistant urinary-tract infections in children over 3 months of age.

Tendon damage

Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment; cases have also been reported several months after stopping a quinolone. Healthcare professionals are reminded that:

- quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use;
- the risk of tendon damage is increased by the concomitant use of corticosteroids;
- if tendinitis is suspected, the quinolone should be discontinued immediately.

Contra-indications Quinolone hypersensitivity.

Pregnancy Quinolones should be avoided in pregnancy because they have been shown to cause arthropathy in *animal* studies; safer alternatives are available; however, a single dose of ciprofloxacin may be used for the prevention of a secondary case of meningococcal meningitis.

Side-effects Side-effects of the quinolones include nausea, vomiting, diarrhoea (rarely antibiotic-associated colitis), headache, and dizziness. Less frequent side-effects include dyspepsia, abdominal pain, anorexia, sleep disturbances, asthenia, confusion, anxiety, depression, hallucinations, tremor, blood disorders (including eosinophilia, leucopenia, thrombocytopenia), arthralgia, myalgia, rash (very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), disturbances in vision and taste. Other side-effects reported rarely or very rarely include hepatic dysfunction (including jaundice and hepatitis), hypotension, vasculitis, dyspnoea, convulsions, psychoses, symptoms of peripheral neuropathy (sometimes irreversible), renal failure, interstitial nephritis, tendon inflammation and damage (see also

Tendon Damage above), photosensitivity, disturbances in hearing and smell. The drug should be **discontinued** if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur.

CIPROFLOXACIN

Cautions see notes above; avoid excessive alkalinity of urine and ensure adequate fluid intake (risk of crystalluria); **interactions:** Appendix 1 (quinolones)
Skilled tasks May impair performance of skilled tasks (e.g. driving)

Contra-indications see notes above

Renal impairment reduce dose if estimated glomerular filtration rate less than 30 mL/minute/ 1.73 m^2 —consult product literature

Pregnancy see notes above

Breast-feeding amount probably too small to be harmful but manufacturer advises avoid

Side-effects see notes above; also flatulence, pain and phlebitis at injection site; *rarely* dysphagia, pancreatitis, chest pain, tachycardia, syncope, oedema, hot flushes, abnormal dreams, sweating, hyperglycaemia, hypoglycaemia, and erythema nodosum; *very rarely* movement disorders, tinnitus, intracranial hypertension, vasculitis, and tenosynovitis; *also reported* peripheral neuropathy and polyneuropathy

Licensed use licensed for use in children over 1 year for complicated urinary-tract infections, for pseudomonas lower respiratory-tract infections in cystic fibrosis, for prophylaxis and treatment of inhalational anthrax; licensed for use in children over 1 year for other infections where the benefit is considered to outweigh the potential risks; not licensed for use in children for gastro-intestinal anthrax; not licensed for use in children for prophylaxis of meningococcal meningitis; not licensed for use in children under 1 year of age

Indications and dose

Complicated urinary-tract infections

• By mouth

Neonate 10 mg/kg twice daily

Child 1 month–18 years 10 mg/kg twice daily; dose doubled in severe infection (max. 750 mg twice daily)

• By intravenous infusion over 60 minutes

Neonate 6 mg/kg every 12 hours

Child 1 month–18 years 6 mg/kg every 8 hours; increased to 10 mg/kg every 8 hours in severe infection (max. 400 mg every 8 hours)

Severe respiratory-tract infections, gastro-intestinal infections; see notes above

• By mouth

Neonate 15 mg/kg twice daily

Child 1 month–18 years 20 mg/kg (max. 750 mg) twice daily

• By intravenous infusion over 60 minutes

Neonate 10 mg/kg every 12 hours

Child 1 month–18 years 10 mg/kg (max. 400 mg) every 8 hours

Pseudomonas lower respiratory-tract infection in cystic fibrosis

• By mouth

Child 1 month–18 years 20 mg/kg (max. 750 mg) twice daily

• By intravenous infusion over 60 minutes

Child 1 month–18 years 10 mg/kg (max. 400 mg) every 8 hours

Gonorrhoea

• By mouth

Child 12–18 years 500 mg as a single dose

Anthrax (treatment and post-exposure prophylaxis, see notes above)

• By mouth

Child 1 month–18 years 15 mg/kg (max. 500 mg) twice daily

• By intravenous infusion over 60 minutes

Child 1 month–18 years 10 mg/kg (max. 400 mg) every 12 hours

Fistulating Crohn's disease section 1.5

Eye infections section 11.3.1

Prophylaxis of meningococcal meningitis Table 2, section 5.1

Ciprofloxacin (Non-proprietary) (PoM)

Tablets, ciprofloxacin (as hydrochloride) 100 mg, net price 6-tab pack = £1.26; 250 mg, 10-tab pack = 84p, 20-tab pack = £1.48; 500 mg, 10-tab pack = 98p, 20-tab pack = £1.47; 750 mg, 10-tab pack = £8.00. Label: 7, 9, 25, counselling, driving

Intravenous infusion, ciprofloxacin (as lactate)

2 mg/mL, net price 50-mL bottle = £7.57, 100-mL bottle = £14.49, 200-mL bottle = £19.79

Ciproxin® (Bayer) (PoM)

Tablets, all f/c, ciprofloxacin (as hydrochloride) 250 mg (scored), net price 10-tab pack = £6.59; 500 mg (scored), 10-tab pack = £12.49; 750 mg, 10-tab pack = £17.78. Label: 7, 9, 25, counselling, driving

Suspension, strawberry-flavoured, ciprofloxacin for reconstitution with diluent provided, 250 mg/5 mL, net price 100 mL = £19.80. Label: 7, 9, 25, counselling, driving

Intravenous infusion, ciprofloxacin (as lactate)

2 mg/mL, in sodium chloride 0.9%, net price 50-mL bottle = £7.61, 100-mL bottle = £15.01, 200-mL bottle = £22.85

Electrolytes Na⁺ 15.4 mmol/100-mL bottle

NALIDIXIC ACID

Cautions see notes above; avoid in acute porphyria (section 9.8.2); false positive urinary glucose (if tested for reducing substances); monitor blood counts, renal and liver function if treatment exceeds 2 weeks; **interactions:** Appendix 1 (quinolones)

Contra-indications see notes above

Hepatic impairment manufacturer advises caution in liver disease

Renal impairment use with caution; avoid if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Pregnancy see notes above

Breast-feeding risk to infant very small but one case of haemolytic anaemia reported

Side-effects see notes above; also reported toxic psychosis, increased intracranial pressure, cranial nerve palsy, peripheral neuropathy, metabolic acidosis

Licensed use not licensed for use in children under 3 months of age

Indications and dose

Urinary tract infection resistant to other antibiotics

• By mouth

Child 3 months–12 years 12.5 mg/kg 4 times daily for 7 days, reduced to 7.5 mg/kg 4 times daily in prolonged therapy or 15 mg/kg twice daily for prophylaxis

Child 12–18 years 900 mg 4 times daily for 7 days, reduced in chronic infections to 600 mg 4 times daily

Nalidixic acid (Rosemont) (PoM)

Suspension, pink, nalidixic acid 300 mg/5 mL, net price 150 mL (raspberry- and strawberry-flavoured) = £17.00. Label: 9, 11

Excipients include sucrose 450 mg/5 mL

5.1.13 Urinary-tract infections

Urinary-tract infection is more common in adolescent girls than in boys; when it occurs in adolescent boys there is frequently an underlying abnormality of the renal tract. Recurrent episodes of infection are an indication for radiological investigation especially in children in whom untreated pyelonephritis may lead to permanent kidney damage.

Escherichia coli is the most common cause of urinary-tract infection; *Staphylococcus saprophyticus* is also common in sexually active young women. Less common causes include *Proteus* and *Klebsiella* spp. *Pseudomonas aeruginosa* infections usually occur in the hospital setting and may be associated with functional or anatomical abnormalities of the renal tract. *Staphylococcus epidermidis* and *Enterococcus faecalis* infection may complicate catheterisation or instrumentation.

A specimen of urine should be collected for culture and sensitivity testing before starting antibacterial therapy;

- in children under 3 years of age;
- in children with suspected upper urinary-tract infection, complicated infection, or recurrent infection;
- if resistant organisms are suspected;
- if urine dipstick testing gives a single positive result for leucocyte esterase or nitrite;
- if clinical symptoms are not consistent with results of dipstick testing;
- in pregnant women.

Treatment should not be delayed while waiting for results. The antibacterial chosen should reflect current local bacterial sensitivity to antibacterials.

Urinary-tract infections in children require prompt antibacterial treatment to minimise the risk of renal scarring. Uncomplicated 'lower' urinary-tract infections in children over 3 months of age can be treated with trimethoprim, nitrofurantoin, a first generation cephalosporin, or amoxicillin for 3 days; children should be reassessed if they continue to be unwell 24–48 hours after the initial assessment.

Acute pyelonephritis in children over 3 months of age can be treated with a first generation cephalosporin or co-amoxiclav for 7–10 days. If the patient is severely ill, then the infection is best treated initially by intravenous injection of a broad-spectrum antibacterial such as cefotaxime or co-amoxiclav; gentamicin is an alternative.

Children under 3 months of age should be transferred to hospital and treated initially with intravenous antibacterials such as ampicillin with gentamicin, or cefotaxime alone, until the infection responds; full doses of oral antibacterials are then given for a further period.

Resistant infections Widespread bacterial resistance to ampicillin, amoxicillin, and trimethoprim has been reported. Alternatives for resistant organisms include co-amoxiclav (amoxicillin with clavulanic acid), an oral cephalosporin, pivmecillinam, or a quinolone.

Antibacterial prophylaxis Recurrent episodes of infection are an indication for imaging tests. *Antibacterial prophylaxis* with low doses of trimethoprim or nitrofurantoin may be considered for children with recurrent infection, significant urinary-tract anomalies, or significant kidney damage. Nitrofurantoin is contraindicated in children under 3 months of age because of the theoretical possibility of haemolytic anaemia.

Pregnancy Urinary-tract infection in pregnancy may be asymptomatic and requires prompt treatment to prevent progression to acute pyelonephritis. Penicillins and cephalosporins are suitable for treating urinary-tract infection during pregnancy. Nitrofurantoin may also be used but it should be avoided at term. Sulfonamides, quinolones, and tetracyclines should be avoided during pregnancy; trimethoprim should also preferably be avoided particularly in the first trimester.

Renal impairment In renal failure antibacterials normally excreted by the kidney accumulate with resultant toxicity unless the dose is reduced. This applies especially to the aminoglycosides which should be used with great caution; tetracyclines, methamine, and nitrofurantoin should be avoided altogether.

NITROFURANTOIN

Cautions anaemia; diabetes mellitus; electrolyte imbalance; vitamin B and folate deficiency; pulmonary disease; on long-term therapy, monitor liver function and monitor for pulmonary symptoms (discontinue if deterioration in lung function); susceptibility to peripheral neuropathy; false positive urinary glucose (if tested for reducing substances); urine may be coloured yellow or brown; **interactions:** Appendix 1 (nitrofurantoin)

Contra-indications infants less than 3 months old, G6PD deficiency (section 9.1.5), acute porphyria (section 9.8.2)

Hepatic impairment use with caution; cholestatic jaundice and chronic active hepatitis reported

Renal impairment avoid if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²; risk of peripheral neuropathy; ineffective because of inadequate urine concentrations

Pregnancy avoid at term—may produce neonatal haemolysis

Breast-feeding avoid; only small amounts in milk but enough to produce haemolysis in G6PD-deficient infants (section 9.1.5)

Side-effects anorexia, nausea, vomiting, and diarrhoea; acute and chronic pulmonary reactions (pulmonary fibrosis reported; possible association with lupus erythematosus-like syndrome); peripheral neuropathy; also reported, hypersensitivity reactions (including angioedema, anaphylaxis, sialadenitis, urticaria, rash and pruritus); rarely, cholestatic jaundice, hepatitis, exfoliative dermatitis, erythema multiforme, pancreatitis, arthralgia, blood disorders (including agranulocytosis, thrombocytopenia, and aplastic anaemia), benign intracranial hypertension, and transient alopecia

Indications and dose

Acute uncomplicated urinary-tract infection

• By mouth

Child 3 months–12 years 750 micrograms/kg 4 times daily for 3–7 days

Child 12–18 years 50 mg 4 times daily for 3–7 days; increased to 100 mg 4 times daily in severe chronic recurrent infections

Prophylaxis of urinary-tract infection (but see Cautions above)

Table 2, section 5.1

Nitrofurantoin (Non-proprietary) (PoM)

Tablets, nitrofurantoin 50 mg, net price 28-tab pack = £24.35; 100 mg, 28-tab pack = £7.07 Label: 9, 14, 21

Oral suspension, nitrofurantoin 25 mg/5 mL, net price 300 mL = £195.83. Label: 9, 14, 21

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Macrobid[®] (AMCo) (PoM)

Capsules, yellow/white, nitrofurantoin 50 mg (as macrocrystals), net price 30-cap pack = £3.66; 100 mg (yellow/white), 30-cap pack = £6.91. Label: 9, 14, 21

Modified release

Macrobid[®] (AMCo) (PoM)

Capsules, m/r, blue/yellow, nitrofurantoin 100 mg (as nitrofurantoin macrocrystals and nitrofurantoin monohydrate). Net price 14-cap pack = £9.50. Label: 9, 14, 21, 25

Dose

Uncomplicated urinary-tract infection

Child 12–18 years 1 capsule twice daily with food

Genito-urinary surgical prophylaxis

Child 12–18 years 1 capsule twice daily on day of procedure and for 3 days after

5.2 Antifungal drugs

5.2.1 Triazole antifungals

5.2.2 Imidazole antifungals

5.2.3 Polyene antifungals

5.2.4 Echinocandin antifungals

5.2.5 Other antifungals

Treatment of fungal infections

The systemic treatment of common fungal infections is outlined below; specialist treatment is required in most forms of systemic or disseminated fungal infections. For local treatment of fungal infections, see section 7.2.2 (genital), section 7.4.4 (bladder), section 11.3.2 (eye), section 12.1.1 (ear), section 12.3.2 (oropharynx), and section 13.10.2 (skin).

Aspergillosis Aspergillosis most commonly affects the respiratory tract but in severely immunocompromised patients, invasive forms can affect the heart, brain, and skin. **Voriconazole** (section 5.2.1) is the treatment of choice for aspergillosis; **liposomal amphotericin** (section 5.2.3) is an alternative first-line treatment when voriconazole cannot be used. **Caspofungin** (section 5.2.4) or **itraconazole** (section 5.2.1) can be used in patients who are refractory to, or intolerant of voriconazole and liposomal amphotericin. Itraconazole is also used for the treatment of chronic pulmonary aspergillosis or as an adjunct in the treatment of allergic bronchopulmonary aspergillosis.

Candidiasis Many superficial candidal infections, including infections of the skin (section 13.10.2), are treated locally. Systemic antifungal treatment is required in widespread or intractable infection. Vaginal candidiasis can be treated with locally acting antifungals (section 7.2.2); alternatively, **fluconazole** (section 5.2.1) can be given by mouth.

Oropharyngeal candidiasis generally responds to topical therapy (section 12.3.2). Fluconazole is given by mouth for unresponsive infections; it is reliably absorbed and is effective. **Itraconazole** (section 5.2.1) may be used for infections that do not respond to fluconazole. Topical therapy may not be adequate in immunocompromised children and an oral triazole antifungal is preferred.

For *invasive or disseminated candidiasis*, either **amphotericin** (section 5.2.3) by intravenous infusion or an **echinocandin** (section 5.2.4) can be used. **Fluconazole** (section 5.2.1) is an alternative for *Candida albicans* infection in clinically stable children who have not received an azole antifungal recently. Amphotericin should be considered for the initial treatment of CNS candidiasis. **Voriconazole** (section 5.2.1) can be used for infections caused by fluconazole-resistant *Candida* spp. when oral therapy is required, or in children intolerant of amphotericin or an echinocandin. In refractory cases, **flucytosine** (section 5.2.5) can be used with intravenous amphotericin.

Cryptococcosis Cryptococcosis is uncommon but infection in the immunocompromised, especially HIV-positive children, can be life-threatening; cryptococcal meningitis is the most common form of fungal meningitis. The treatment of choice in cryptococcal meningitis is **amphotericin** (section 5.2.3) by intravenous infusion with **flucytosine** (section 5.2.5) by intravenous infusion for 2 weeks, followed by **fluconazole** (section 5.2.1) by

mouth for 8 weeks or until cultures are negative. In cryptococcosis, fluconazole is sometimes given alone as an alternative in HIV-positive children with mild localised infection or in those who cannot tolerate amphotericin. Following successful treatment, fluconazole can be used for prophylaxis against relapse until immunity recovers.

Histoplasmosis Histoplasmosis is rare in temperate climates; it can be life-threatening, particularly in HIV-infected children. **Itraconazole** (section 5.2.1) can be used for the treatment of immunocompetent children with indolent non-meningeal infection, including chronic pulmonary histoplasmosis. **Amphotericin** (section 5.2.3) by intravenous infusion is used for the treatment of fulminant or severe infections, and may be followed by a course of itraconazole by mouth. Following successful treatment, itraconazole can be used for prophylaxis against relapse until immunity recovers.

Skin and nail infections Mild localised fungal infections of the skin (including tinea corporis, tinea cruris, and tinea pedis) respond to topical therapy (section 13.10.2). Systemic therapy is appropriate if topical therapy fails, if many areas are affected, or if the site of infection is difficult to treat such as in infections of the nails (onychomycosis) and of the scalp (tinea capitis).

Oral imidazole or triazole antifungals (particularly **itraconazole**) and **terbinafine** are used more frequently than griseofulvin because they have a broader spectrum of activity and require a shorter duration of treatment.

Tinea capitis is treated systemically; additional topical application of an antifungal (section 13.10.2) may reduce transmission. **Griseofulvin** (section 5.2.5) is used for tinea capitis; it is effective against infections caused by *Trichophyton tonsurans* and *Microsporum* spp. **Terbinafine** (section 5.2.5) is used for tinea capitis caused by *T. tonsurans* (unlicensed indication); the role of terbinafine in the management of *Microsporum* infections is uncertain. **Fluconazole** (section 5.2.1) or **itraconazole** (section 5.2.1) are alternatives in the treatment of tinea capitis caused by *T. tonsurans* or *Microsporum* spp. [both unlicensed indications].

Pityriasis versicolor (section 13.10.2) may be treated with **itraconazole** (section 5.2.1) by mouth if topical therapy is ineffective; **fluconazole** (section 5.2.1) by mouth is an alternative. Oral **terbinafine** is not effective for pityriasis versicolor.

Antifungal treatment may not be necessary in asymptomatic children with tinea infection of the nails. If treatment is necessary, a systemic antifungal is more effective than topical therapy. **Terbinafine** (section 5.2.5) and **itraconazole** (section 5.2.1) have largely replaced griseofulvin for the systemic treatment of onychomycosis, particularly of the toenail; they should be used under specialist advice. Although terbinafine is not licensed for use in children, it is considered to be the drug of choice for onychomycosis. Itraconazole can be administered as intermittent 'pulse' therapy. For the role of topical antifungals in the treatment of onychomycosis, see section 13.10.2.

Immunocompromised children Immunocompromised children are at particular risk of fungal infections and may receive antifungal drugs prophylactically; oral triazole antifungals are the drugs of choice for prophylaxis. **Fluconazole** (section 5.2.1) is more reliably absorbed than **itraconazole** (section 5.2.1), but fluconazole is not effective against *Aspergillus* spp. Itraconazole

is preferred in patients at risk of invasive aspergillosis. **Micafungin** (section 5.2.4) can be used for prophylaxis of candidiasis in patients undergoing haematopoietic stem cell transplantation when fluconazole or itraconazole cannot be used.

Amphotericin (section 5.2.3) by intravenous infusion or **caspofungin** (section 5.2.4) is used for the empirical treatment of serious fungal infections in immunocompromised children; caspofungin is not effective against fungal infections of the CNS.

5.2.1 Triazole antifungals

For the role of triazole antifungal drugs in the prevention and systemic treatment of fungal infections, see p. 304. **Fluconazole** is very well absorbed after oral administration. It also achieves good penetration into the cerebrospinal fluid to treat fungal meningitis. Fluconazole is excreted largely unchanged in the urine and can be used to treat candiduria.

Itraconazole is active against a wide range of dermatophytes. There is limited information available on use in children. Itraconazole capsules require an acid environment in the stomach for optimal absorption.

Itraconazole has been associated with liver damage and should be avoided or used with caution in children with liver disease; fluconazole is less frequently associated with hepatotoxicity.

Voriconazole is a broad-spectrum antifungal drug which is licensed in adults for the treatment of life-threatening infections.

FLUCONAZOLE

Cautions concomitant use with hepatotoxic drugs, monitor liver function with high doses or extended courses—discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis); susceptibility to QT interval prolongation; **interactions:** Appendix 1 (antifungals, triazole)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment toxicity with related drugs

Renal impairment usual initial dose then halve subsequent doses if estimated glomerular filtration rate less than 50 mL/minute/1.73m²

Pregnancy manufacturer advises avoid—multiple congenital abnormalities reported with long-term high doses

Breast-feeding present in milk but amount probably too small to be harmful

Side-effects nausea, abdominal discomfort, diarrhoea, flatulence, headache, rash (discontinue treatment or monitor closely if infection invasive or systemic); less frequently dyspepsia, vomiting, taste disturbance, hepatic disorders, angioedema, anaphylaxis, dizziness, seizures, alopecia, pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome (severe cutaneous reactions more likely in AIDS patients), hyperlipidaemia, leucopenia, thrombocytopenia, and hypokalaemia reported

Licensed use not licensed for tinea infections in children, or for vaginal candidiasis in girls under 16 years, or for prevention of relapse of cryptococcal meningitis after completion of primary therapy in children with AIDS

Indications and dose**Mucosal candidiasis (except genital)**

- By mouth or by intravenous infusion

Neonate under 2 weeks 3–6 mg/kg on first day then 3 mg/kg every 72 hours

Neonate 2–4 weeks 3–6 mg/kg on first day then 3 mg/kg every 48 hours

Child 1 month–12 years 3–6 mg/kg on first day then 3 mg/kg (max. 100 mg) daily for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections)

Child 12–18 years 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections)

Vaginal candidiasis (see also Recurrent Vulvovaginal Candidiasis, section 7.2.2)

- By mouth

Child under 16 years (post-puberty) a single dose of 150 mg

Child 16–18 years a single dose of 150 mg

Candidal balanitis

- By mouth

Child 16–18 years a single dose of 150 mg

Tinea pedis, corporis, cruris, pityriasis versicolor, and dermal candidiasis

- By mouth

Child 1 month–18 years 3 mg/kg (max. 50 mg) daily for 2–4 weeks (for up to 6 weeks in tinea pedis); max. duration of treatment 6 weeks

Tinea capitis

- By mouth

Child 1–18 years 6 mg/kg (max. 300 mg) daily for 2–4 weeks

Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis)

- By mouth or by intravenous infusion

Neonate under 2 weeks 6–12 mg/kg every 72 hours, treatment continued according to response (at least 8 weeks for cryptococcal meningitis)

Neonate 2–4 weeks 6–12 mg/kg every 48 hours, treatment continued according to response (at least 8 weeks for cryptococcal meningitis)

Child 1 month–18 years 6–12 mg/kg (max. 800 mg) daily, treatment continued according to response (at least 8 weeks for cryptococcal meningitis)

Prevention of relapse of cryptococcal meningitis in HIV-infected patients after completion of primary therapy

- By mouth or by intravenous infusion

Child 1 month–18 years 6 mg/kg (max. 200 mg) daily

Prevention of fungal infections in immunocompromised patients

- By mouth or by intravenous infusion

Neonate under 2 weeks according to extent and duration of neutropenia, 3–12 mg/kg every 72 hours

Neonate 2–4 weeks according to extent and duration of neutropenia, 3–12 mg/kg every 48 hours

Child 1 month–18 years according to extent and duration of neutropenia, 3–12 mg/kg (max. 400 mg) daily; 12 mg/kg (max. 400 mg) daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range

Administration for intravenous infusion, give over 10–30 minutes; do not exceed an infusion rate of 5–10 mL/minute

Fluconazole (Non-proprietary) (PoM)

¹**Capsules**, fluconazole 50 mg, net price 7-cap pack = £1.00; 150 mg, single-capsule pack = 94p; 200 mg, 7-cap pack = £8.38. Label: 9, (50 and 200 mg)

Dental prescribing on NHS Fluconazole Capsules 50 mg may be prescribed

Intravenous infusion, fluconazole 2 mg/mL, net price 25-mL bottle = £7.31; 100-mL bottle = £27.45; 50-mL infusion bag = £2.70; 100-mL infusion bag = £27.82

Diflucan® (Pfizer) (PoM)

¹**Capsules**, fluconazole 50 mg (blue/white), net price 7-cap pack = £16.61; 150 mg (blue), single-capsule pack = £7.12; 200 mg (purple/white), 7-cap pack = £66.42. Label: 9, (50 and 200 mg)

Oral suspension, orange-flavoured, fluconazole for reconstitution with water, 50 mg/5 mL, net price 35 mL = £16.61; 200 mg/5 mL, 35 mL = £66.42. Label: 9

Dental prescribing on NHS May be prescribed as Fluconazole Oral Suspension 50 mg/5 mL

Intravenous infusion, fluconazole 2 mg/mL in sodium chloride intravenous infusion 0.9%, net price 100-mL bottle = £29.28

Electrolytes Na⁺ 15 mmol/100-mL bottle

ITRACONAZOLE

Cautions absorption reduced in AIDS and neutropenia (monitor plasma-itraconazole concentration and increase dose if necessary); susceptibility to congestive heart failure (see also Heart Failure, below); **interactions:** Appendix 1 (antifungals, triazole) **Hepatotoxicity** Potentially life-threatening hepatotoxicity reported very rarely—discontinue if signs of hepatitis develop. Avoid or use with caution if history of

1. Capsules can be sold to the public for vaginal candidiasis and associated candidal balanitis in those aged 16–18 years, in a container or packaging containing not more than 150 mg and labelled to show a max. dose of 150 mg

hepatotoxicity with other drugs or in active liver disease. Monitor liver function if treatment continues for longer than one month, if receiving other hepatotoxic drugs, if history of hepatotoxicity with other drugs, or in hepatic impairment

Counselling Children or their carers should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine develop

Heart failure

Following reports of heart failure, caution is advised when prescribing itraconazole to patients at high risk of heart failure. Those at risk include:

- patients receiving high doses and longer treatment courses;
- patients with cardiac disease;
- patients with chronic lung disease associated with pulmonary hypertension;
- patients receiving treatment with negative inotropic drugs, e.g. calcium channel blockers.

Itraconazole should be avoided in patients with ventricular dysfunction or a history of heart failure unless the infection is serious.

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment use only if potential benefit outweighs risk of hepatotoxicity (see Hepatotoxicity above); dose reduction may be necessary

Renal impairment risk of congestive heart failure; bioavailability of oral formulations possibly reduced; use intravenous infusion with caution if estimated glomerular filtration rate 30–80 mL/minute/1.73 m² (monitor renal function); avoid intravenous infusion if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy manufacturer advises use only in life-threatening situations (toxicity at high doses in animal studies); ensure effective contraception during treatment and until the next menstrual period following end of treatment

Breast-feeding small amounts present in milk—may accumulate; manufacturer advises avoid

Side-effects nausea, vomiting, taste disturbances, abdominal pain, diarrhoea, hepatitis (see Hepatotoxicity above), blood pressure changes, dyspnoea, cough, headache, hypokalaemia, rash; *less commonly* dyspepsia, flatulence, constipation, oedema, dizziness, peripheral neuropathy (discontinue treatment), menstrual disorder, myalgia; *rarely* pancreatitis, heart failure (see Cautions above), hypertriglyceridaemia, erectile dysfunction, urinary frequency, leucopenia, visual disturbances, tinnitus, deafness, alopecia, photosensitivity, toxic epidermal necrolysis, Stevens-Johnson syndrome; also reported, confusion, drowsiness, tremor, thrombocytopenia, renal impairment, arthralgia; *with intravenous injection* hyperglycaemia

Licensed use not licensed for use in children (age range not specified by manufacturer)

Indications and dose

Oropharyngeal candidiasis

• By mouth

Child 1 month–12 years 3–5 mg/kg once daily; max. 100 mg daily (200 mg daily in AIDS or neutropenia) for 15 days

Child 12–18 years 100 mg once daily (200 mg once daily in AIDS or neutropenia) for 15 days

Pityriasis versicolor

• By mouth

Child 1 month–12 years 3–5 mg/kg (max. 200 mg) once daily for 7 days

Child 12–18 years 200 mg once daily for 7 days

Tinea corporis and tinea cruris

• By mouth

Child 1 month–12 years 3–5 mg/kg (max. 100 mg) once daily for 15 days

Child 12–18 years *either* 100 mg once daily for 15 days *or* 200 mg once daily for 7 days

Tinea pedis and tinea manuum

• By mouth

Child 1 month–12 years 3–5 mg/kg (max. 100 mg) once daily for 30 days

Child 12–18 years *either* 100 mg once daily for 30 days *or* 200 mg twice daily for 7 days

Tinea capitis

• By mouth

Child 1–18 years 3–5 mg/kg (max. 200 mg) daily for 2–6 weeks

Onychomycosis

• By mouth

Child 1–12 years course ('pulse') of 5 mg/kg (max. 200 mg) daily for 7 days; subsequent courses repeated after 21 day intervals; fingernails 2 courses, toenails 3 courses

Child 12–18 years *either* 200 mg once daily for 3 months *or* course ('pulse') of 200 mg twice daily for 7 days, subsequent courses repeated after 21-day intervals; fingernails 2 courses, toenails 3 courses

Systemic aspergillosis, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective (limited information available)

• By mouth

Child 1 month–18 years 5 mg/kg (max. 200 mg) once daily; increased in invasive or disseminated disease and in cryptococcal meningitis to 5 mg/kg (max. 200 mg) twice daily

• By intravenous infusion

Child 1 month–18 years 2.5 mg/kg (max. 200 mg) every 12 hours for 2 days, then 2.5 mg/kg (max. 200 mg) once daily for max. 12 days

Histoplasmosis

• By mouth

Child 1 month–18 years 5 mg/kg (max. 200 mg) 1–2 times daily

Maintenance in HIV-infected patients to prevent relapse of underlying fungal infection and prophylaxis in neutropenia when standard therapy inappropriate

• By mouth

Child 1 month–18 years 5 mg/kg (max. 200 mg) once daily, increased to 5 mg/kg (max. 200 mg)

twice daily if low plasma-itraconazole concentration (see Cautions)

Prophylaxis of deep fungal infections (when standard therapy inappropriate) in patients with haematological malignancy or undergoing bone-marrow transplantation who are expected to become neutropenic

• **By mouth (liquid preparation only)**

Child 1 month–18 years 2.5 mg/kg twice daily starting before transplantation or before chemotherapy (taking care to avoid interaction with cytotoxic drugs) and continued until neutrophil count recovers

Administration For intravenous infusion, dilute 250 mg with 50 mL Sodium Chloride 0.9% and give requisite dose through an in-line filter (0.2 micron) over 60 minutes

Itraconazole (Non-proprietary) (PoM)

Capsules, enclosing coated beads, itraconazole 100 mg, net price 15-cap pack = £4.30. Label: 5, 9, 21, 25, counselling, hepatotoxicity

Sporanox® (Janssen) (PoM)

Capsules, blue/pink, enclosing coated beads, itraconazole 100 mg, net price 4-cap pack = £3.67; 15-cap pack = £13.77; 28-cap pack (*Sporanox®-Pulse*) = £25.72; 60-cap pack = £55.10. Label: 5, 9, 21, 25, counselling, hepatotoxicity

Oral liquid, sugar-free, cherry-flavoured, itraconazole 10 mg/mL, net price 150 mL (with 10-mL measuring cup) = £58.34. Label: 9, 23, counselling, administration, hepatotoxicity

Counselling Do not take with food; swish around mouth and swallow, do not rinse afterwards

Concentrate for intravenous infusion, itraconazole 10 mg/mL. For dilution before use. Net price 25-mL amp (with infusion bag and filter) = £79.71

Excipients include propylene glycol

VORICONAZOLE

Cautions electrolyte disturbances, cardiomyopathy, bradycardia, symptomatic arrhythmias, history of QT interval prolongation, concomitant use with other drugs that prolong QT interval; avoid exposure to sunlight; patients at risk of pancreatitis; monitor renal function; **interactions:** Appendix 1 (antifungals, triazole)

Hepatotoxicity Hepatitis, cholestasis, and fulminant hepatic failure reported uncommonly usually in first 10 days; risk increased in patients with haematological malignancy. Monitor liver function before treatment and during treatment

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment **Child 2–12 years** no information available. **Child 12–18 years** in mild to moderate hepatic cirrhosis use usual initial dose then halve subsequent doses; no information available for severe hepatic cirrhosis—manufacturer advises use only if potential benefit outweighs risk. See also Hepatotoxicity above.

Renal impairment **Child 2–12 years** no information available. **Child 12–18 years** intravenous vehicle may accumulate if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²—use intravenous infusion only if potential benefit outweighs risk, and monitor renal function; alternatively, use tablets or oral suspension (no dose adjustment required)

Pregnancy toxicity in *animal* studies—manufacturer advises avoid unless potential benefit outweighs risk; effective contraception required during treatment

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, abdominal pain, diarrhoea, jaundice (see Hepatotoxicity above), oedema, hypotension, chest pain, respiratory distress syndrome, sinusitis, headache, dizziness, asthenia, anxiety, depression, confusion, agitation, hallucinations, paraesthesia, tremor, influenza-like symptoms, hypoglycaemia, haematuria, blood disorders (including anaemia, thrombocytopenia, leucopenia, pancytopenia), acute renal failure, hypokalaemia, visual disturbances, (including altered perception, blurred vision, and photophobia), rash, pruritus, photosensitivity, alopecia, cheilitis, injection-site reactions; *less commonly* dyspepsia, duodenitis, cholecystitis, pancreatitis, hepatitis (see Hepatotoxicity above), constipation, arrhythmias (including QT interval prolongation), syncope, hyponatraemia, raised serum cholesterol, hypersensitivity reactions (including flushing), ataxia, nystagmus, hypoaesthesia, adrenocortical insufficiency, arthritis, blepharitis, optic neuritis, scleritis, glossitis, gingivitis, psoriasis, Stevens-Johnson syndrome; *rarely* pseudomembranous colitis, taste disturbances (more common with oral suspension), convulsions, extrapyramidal effects, insomnia, tinnitus, hearing disturbances, hypertonia, hypothyroidism, hyperthyroidism, discoid lupus erythematosus, toxic epidermal necrolysis, pseudoporphyria, retinal haemorrhage, optic atrophy; also reported squamous cell carcinoma of skin (particularly in presence of phototoxicity), periostitis (particularly in transplant patients)

Indications and dose

Invasive aspergillosis; serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*)

• **By mouth**

Child 2–12 years (transfer to oral suspension after initial intravenous therapy) 9 mg/kg every 12 hours (reduced in steps of 1 mg/kg if not tolerated; increased in steps of 1 mg/kg if inadequate response); max. 350 mg every 12 hours (reduced in steps of 50 mg if not tolerated; increased in steps of 50 mg if inadequate response)

Child 12–15 years

Body-weight under 50 kg dose as for child 2–12 years

Body-weight over 50 kg dose as for child 15–18 years and body-weight over 40 kg

Child 15–18 years, body-weight under 40 kg

200 mg every 12 hours for 2 doses then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours

Child 15–18 years, body-weight over 40 kg

400 mg every 12 hours for 2 doses then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours

• **By intravenous infusion**

Child 2–12 years 9 mg/kg every 12 hours for 2 doses then 8 mg/kg every 12 hours (reduced in steps of 1 mg/kg if not tolerated; increased in steps of 1 mg/kg if inadequate response) for max. 6 months

Child 12–15 years**Body-weight under 50 kg** dose as for child 2–12 years**Body-weight over 50 kg** dose as for child 15–18 years**Child 15–18 years** 6 mg/kg every 12 hours for 2 doses then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for max. 6 months

Administration For *intravenous infusion*, reconstitute each 200 mg with 19 mL Water for Injections or Sodium Chloride 0.9% to produce a 10 mg/mL solution; dilute dose to concentration of 0.5–5 mg/mL with Glucose 5% or Sodium Chloride 0.9% and give at a rate not exceeding 3 mg/kg/hour

Vfend® (Pfizer) (POM)

Tablets, f/c, voriconazole 50 mg, net price 28-tablet pack = £275.68; 200 mg, 28-tab pack = £1102.74. Label: 9, 11, 23

Oral suspension, voriconazole 200 mg/5 mL when reconstituted with water, net price 75 mL (orange-flavoured) = £551.37. Label: 9, 11, 23

Intravenous infusion, powder for reconstitution, voriconazole, net price 200-mg vial = £77.14; 200-mg vial (with solvent) = £77.14

Excipients include sulfobutylether beta cyclodextrin sodium (risk of accumulation in renal impairment)

Electrolytes Na⁺ 9.47 mmol/vial

5.2.2 Imidazole antifungals

The imidazole antifungals include clotrimazole, econazole, ketoconazole, and tioconazole. They are used for the local treatment of vaginal candidiasis (section 7.2.2) and for dermatophyte infections (section 13.10.2).

CHMP advice**Ketoconazole (July 2013)**

The CHMP has recommended that the marketing authorisation for oral ketoconazole should be suspended. The CHMP concluded that the risk of hepatotoxicity associated with oral ketoconazole is greater than the benefit in treating fungal infections. Doctors should review children who are being treated with oral ketoconazole for fungal infections, with a view to stopping treatment or choosing an alternative treatment. Children with a prescription of oral ketoconazole for fungal infections should be referred back to their doctors.

Topical products containing ketoconazole are not affected by this advice.

Miconazole (section 12.3.2) can be used locally for oral infections; it is also effective in intestinal infections. Systemic absorption may follow use of miconazole oral gel and may result in significant drug interactions.

5.2.3 Polyene antifungals

The polyene antifungals include amphotericin and nystatin; neither drug is absorbed when given by mouth. Nystatin is used for oral, oropharyngeal, and perioral infections by local application in the mouth (section 12.3.2). Nystatin is also used for *Candida albicans* infection of the skin (section 13.10.2)

Amphotericin by intravenous infusion is used for the treatment of systemic fungal infections and is active

against most fungi and yeasts. It is highly protein bound and penetrates poorly into body fluids and tissues. When given parenterally amphotericin is toxic and side-effects are common. Lipid formulations of amphotericin (*Abelcet®* and *AmBisome®*) are significantly less toxic and are recommended when the conventional formulation of amphotericin is contra-indicated because of toxicity, especially nephrotoxicity, or when response to conventional amphotericin is inadequate; lipid formulations are more expensive. For the role of amphotericin in the systemic treatment of fungal infections, see p. 304.

AMPHOTERICIN (Amphotericin B)

Cautions when given parenterally, toxicity common (close supervision necessary and close observation required for at least 30 minutes after test dose; see Anaphylaxis below); hepatic and renal function tests, blood counts and plasma electrolyte (including plasma-potassium and magnesium concentration) monitoring required; corticosteroids (avoid except to control reactions); avoid rapid infusion (risk of arrhythmias); **interactions:** Appendix 1 (amphotericin)

Anaphylaxis Anaphylaxis can occur with any intravenous amphotericin product and a test dose is advisable before the first infusion in children over 1 month of age; the patient should be carefully observed for at least 30 minutes after the test dose. Prophylactic antipyretics or hydrocortisone should only be used in patients who have previously experienced acute adverse reactions (in whom continued treatment with amphotericin is essential)

Renal impairment use only if no alternative; nephrotoxicity may be reduced with use of lipid formulation

Pregnancy not known to be harmful, but manufacturers advise avoid unless potential benefit outweighs risk

Breast-feeding no information available

Side-effects nausea, vomiting, abdominal pain, diarrhoea, cardiovascular effects (including arrhythmias, blood pressure changes, chest pain), dyspnoea, headache, febrile reactions, electrolyte disturbances (including hypokalaemia and hypomagnesaemia), disturbances in renal function (including renal tubular acidosis), abnormal liver function (discontinue treatment), blood disorders (including anaemia, thrombocytopenia), rash; *less commonly* anaphylactoid reactions (see Anaphylaxis, above), bronchospasm, neurological disorders (including convulsions, peripheral neuropathy, tremor, encephalopathy, hearing loss, diplopia); also reported anorexia, myalgia, arthralgia, toxic epidermal necrolysis, Stevens-Johnson syndrome

Licensed use intravenous conventional formulation amphotericin (*Fungizone®*) is licensed for use in children (age range not specified by manufacturer); *AmBisome®* not licensed for use in children under 1 month

Indications and dose**Systemic fungal infections**

- **By intravenous infusion**

See preparations

Note Different preparations of intravenous amphotericin vary in their pharmacodynamics, pharmacokinetics, dosage, and administration; these preparations should **not** be considered interchangeable. To avoid confusion, prescribers should specify the brand to be dispensed.

Fungizone® (Squibb) (PoM)

Intravenous infusion, powder for reconstitution, amphotericin (as sodium deoxycholate complex), net price 50-mg vial = £3.88

Electrolytes $\text{Na}^+ < 0.5 \text{ mmol/l}$ vial

Dose**Systemic fungal infection**● **By intravenous infusion**

Neonate 1 mg/kg once daily, increased if necessary to 1.5 mg/kg daily; after 7 days, may be reduced to 1–1.5 mg/kg on alternate days

Child 1 month–18 years initial test dose of 100 micrograms/kg (max. 1 mg) included as part of first dose of 250 micrograms/kg daily; increased over 2–4 days, if tolerated, to 1 mg/kg daily; in severe infection max. 1.5 mg/kg daily or on alternate days

Note prolonged treatment usually necessary; if interrupted for longer than 7 days, recommence at 250 micrograms/kg daily and increase gradually

Administration For *intravenous infusion*, reconstitute each vial with 10 mL Water for Injections and shake immediately to produce a 5 mg/mL colloidal solution; dilute further in Glucose 5% to a concentration of 100 micrograms/mL (in fluid-restricted children, up to 400 micrograms/mL given via a central line); pH of glucose solution must not be below 4.2 (check each container—consult product literature for details of buffer); infuse over 4–6 hours, or if tolerated over a minimum of 2 hours (initial test dose given over 20–30 minutes); begin infusion immediately after dilution and protect from light; incompatible with Sodium Chloride solutions—flush existing intravenous line with Glucose 5% or use separate line; an in-line filter (pore size no less than 1 micron) may be used

▲ **Lipid formulations****Abelcet®** (TEVA UK) (PoM)

Intravenous infusion, amphotericin 5 mg/mL as lipid complex with L- α -dimyristoylphosphatidylcholine and L- α -dimyristoylphosphatidylglycerol, net price 20-mL vial = £77.50 (hosp. only)

Electrolytes $\text{Na}^+ 3.12 \text{ mmol/l}$ vial

Dose

Severe invasive candidiasis; severe systemic fungal infections in children not responding to conventional amphotericin or to other antifungal drugs or where toxicity or renal impairment precludes conventional amphotericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in children with HIV

● **By intravenous infusion**

Child 1 month–18 years initial test dose of 100 micrograms/kg (max. 1 mg) then 5 mg/kg once daily

Administration for *intravenous infusion*, allow suspension to reach room temperature, shake gently to ensure no yellow settlement, withdraw requisite dose (using 17–19 gauge needle) into one or more 20-mL syringes; replace needle on syringe with a 5-micron filter needle provided (fresh needle for each syringe) and dilute in Glucose 5% to a concentration of 2 mg/mL; preferably give via an infusion pump at a rate of 2.5 mg/kg/hour (initial test dose given over 15 minutes); an in-line filter (pore size no less than 15 micron) may be used; do not use sodium chloride or other electrolyte solutions—flush existing intravenous line with Glucose 5% or use separate line

AmBisome® (Gilead) (PoM)

Intravenous infusion, powder for reconstitution, amphotericin 50 mg encapsulated in liposomes, net price 50-mg vial = £96.69

Electrolytes $\text{Na}^+ < 0.5 \text{ mmol/l}$ vial

Excipients include sucrose 900 mg/vial

Dose

Severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin; suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials

● **By intravenous infusion**

Neonate 1 mg/kg once daily; increased if necessary to 3 mg/kg once daily; max. 5 mg/kg once daily

Child 1 month–18 years initial test dose 100 micrograms/kg (max. 1 mg) then 3 mg/kg once daily; max. 5 mg/kg once daily

Visceral leishmaniasis see section 5.4.5 and product literature

Administration for *intravenous infusion*, reconstitute each vial with 12 mL Water for Injections and shake vigorously to produce a preparation containing 4 mg/mL; withdraw requisite dose from vial and introduce into Glucose 5% or 10% through the 5-micron filter provided, to produce a final concentration of 0.2–2 mg/mL; infuse over 30–60 minutes, or if non-anaphylactic infusion-related reactions occur infuse over 2 hours (initial test dose given over 10 minutes); an in-line filter (pore size no less than 1 micron) may be used; incompatible with sodium chloride solutions—flush existing intravenous line with Glucose 5% or 10%, or use separate line

5.2.4 Echinocandin antifungals

The echinocandin antifungals include **caspofungin** and **micalofungin**. They are only active against *Aspergillus* spp. and *Candida* spp; however micalofungin is not used for the treatment of aspergillosis. Echinocandins are not effective against fungal infections of the CNS. For the role of echinocandin antifungals in the prevention and systemic treatment of fungal infections, see p. 304.

CASPOFUNGIN

Cautions interactions: Appendix 1 (caspofungin)

Hepatic impairment usual initial dose, then use 70% of normal maintenance dose in moderate impairment; no information available for severe impairment

Pregnancy manufacturer advises avoid unless essential—toxicity in animal studies

Breast-feeding present in milk in animal studies—manufacturer advises avoid

Side-effects nausea, diarrhoea, vomiting; tachycardia, hypotension, flushing; dyspnoea; headache; hypokalaemia, hypomagnesaemia; arthralgia; rash, pruritus, sweating, injection-site reactions; *less commonly* abdominal pain, dyspepsia, dysphagia, dry mouth, taste disturbances, anorexia, constipation, flatulence, cholestasis, hepatic dysfunction, ascites, palpitation, arrhythmia, chest pain, heart failure, thrombophlebitis, hypertension, bronchospasm, cough, dizziness, fatigue, paraesthesia, hypoaesthesia, sleep disturbances, tremor, anxiety, disorientation, hyperglycaemia, renal failure, hypocalcaemia, metabolic acidosis, anaemia, thrombocytopenia,

leucopenia, myalgia, muscular weakness, blurred vision, and erythema multiforme; also reported, acute respiratory distress syndrome, anaphylaxis, and hypercalcaemia

Indications and dose

Invasive aspergillosis (see notes above); invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

- By intravenous infusion

Neonate 25 mg/m² once daily

Child 1 month–3 months 25 mg/m² once daily

Child 3 months–1 year 50 mg/m² once daily

Child 1–18 years 70 mg/m² (max. 70 mg) on first day then 50 mg/m² (max. 70 mg) once daily; increased to 70 mg/m² (max. 70 mg) daily if lower dose tolerated but inadequate response

Administration for intravenous infusion, allow vial to reach room temperature; initially reconstitute 50 mg with 10.5 mL Water for Injections to produce a 5.2 mg/mL solution, or reconstitute 70 mg with 10.5 mL Water for Injections to produce a 7.2 mg/mL solution; mix gently to dissolve; dilute requisite dose to a final concentration not exceeding 500 micrograms/mL with Sodium Chloride 0.9%; give over 60 minutes; incompatible with glucose solutions

Candidas® (MSD) (PoM)

Intravenous infusion, powder for reconstitution, caspofungin (as acetate), net price 50-mg vial = £327.67; 70-mg vial = £416.78

MICAFUNGIN

Cautions monitor renal function; interactions:

Appendix 1 (micafungin)

Hepatotoxicity Potentially life-threatening hepatotoxicity reported. Monitor liver function—discontinue if significant and persistent abnormalities in liver function tests develop. Use with caution in hepatic impairment (avoid if severe) or if receiving other hepatotoxic drugs. Risk of hepatic side-effects greater in children under 1 year of age

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe impairment; see also Hepatotoxicity above

Renal impairment use with caution; deterioration in renal function

Pregnancy manufacturer advises avoid unless essential—toxicity in animal studies

Breast-feeding manufacturer advises use only if potential benefit outweighs risk—present in milk in animal studies

Side-effects nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly; blood pressure changes, tachycardia; headache, fever; hypokalaemia, hypomagnesaemia, hypocalcaemia, leucopenia, anaemia, thrombocytopenia, renal failure; rash, phlebitis; less commonly dyspepsia, constipation, hepatitis and cholestasis (see also Hepatotoxicity above), taste disturbances, anorexia, palpitation, bradycardia, flushing, dyspnoea, sleep disturbances, anxiety, confusion, dizziness, tremor, pancytopenia, eosinophilia, hyponatraemia, hyperkalaemia, hypophosphataemia, hyperhidrosis, and pruritus; rarely haemolytic anaemia; also reported disseminated intravascular coagulation, Stevens-Johnson syndrome, toxic epidermal necrolysis

Indications and dose

Invasive candidiasis

- By intravenous infusion

Neonate (seek specialist advice) 2 mg/kg once daily (increased to 4 mg/kg daily if inadequate response) for at least 14 days

Child 1 month–18 years, body-weight under 40 kg 2 mg/kg once daily (increased to 4 mg/kg daily if inadequate response) for at least 14 days

Child 1 month–18 years, body-weight over 40 kg 100 mg once daily (increased to 200 mg daily if inadequate response) for at least 14 days

Oesophageal candidiasis

- By intravenous infusion

Child 16–18 years, body-weight under 40 kg 3 mg/kg once daily

Child 16–18 years, body-weight over 40 kg 150 mg once daily

Prophylaxis of candidiasis in children undergoing bone-marrow transplantation or who are expected to become neutropenic for over 10 days

- By intravenous infusion

Neonate 1 mg/kg once daily; continue for at least 7 days after neutrophil count in desirable range

Child 1 month–18 years, body-weight under 40 kg 1 mg/kg once daily; continue for at least 7 days after neutrophil count in desirable range

Child 1 month–18 years, body-weight over 40 kg 50 mg once daily; continue for at least 7 days after neutrophil count in desirable range

Administration for intravenous infusion reconstitute each vial with 5 mL Glucose 5% or Sodium Chloride 0.9%; gently rotate vial, without shaking, to dissolve; dilute requisite dose to a concentration of 0.5–2 mg/mL with Glucose 5% or Sodium Chloride 0.9%; protect infusion from light; give over 60 minutes

Mycamine® (Astellas) (PoM)

Intravenous infusion, powder for reconstitution, micafungin (as sodium), net price 50-mg vial = £196.08; 100-mg vial = £341.00

5.2.5 Other antifungals

Flucytosine is used with amphotericin in a synergistic combination. Bone marrow depression can occur which limits its use, particularly in children with AIDS; weekly blood counts are necessary during prolonged therapy. Resistance to flucytosine can develop during therapy and sensitivity testing is essential before and during treatment. For the role of flucytosine in the treatment of systemic candidiasis and cryptococcal meningitis, see p. 304.

Griseofulvin is effective for widespread or intractable dermatophyte infections but has been superseded by newer antifungals, particularly for nail infections. Griseofulvin is used in the treatment of tinea capitis. It is the drug of choice for trichophyton infections in children, see p. 305. Duration of therapy is dependent on the site of the infection and may extend to a number of months.

Terbinafine is the drug of choice for fungal nail infections and is also used for ringworm infections where oral treatment is considered appropriate (see p. 305).

FLUCYTOSINE

Cautions blood disorders; liver- and kidney-function tests and blood counts required (weekly in blood disorders); **interactions:** Appendix 1 (flucytosine)

Renal impairment liver- and kidney-function tests and blood counts required weekly; use normal dose every 12 hours if creatinine clearance 20–40 mL/minute; use normal dose every 24 hours if creatinine clearance 10–20 mL/minute; use initial normal dose if creatinine clearance less than 10 mL/minute and then adjust dose according to plasma-flucytosine concentration

Pregnancy teratogenic in *animal* studies; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid

Side-effects nausea, vomiting, diarrhoea, rashes; less frequently cardiotoxicity, confusion, hallucinations, convulsions, headache, sedation, vertigo, alterations in liver function tests (hepatitis and hepatic necrosis reported), and toxic epidermal necrolysis; blood disorders including thrombocytopenia, leucopenia, and aplastic anaemia reported

Pharmacokinetics for plasma-concentration monitoring blood should be taken shortly before starting the next infusion. Plasma concentration for optimum response 25–50 mg/litre (200–400 micromol/litre)—should not be allowed to exceed 80 mg/litre (620 micromol/litre)

Licensed use tablets not licensed

Indications and dose

Systemic yeast and fungal infections, adjunct to amphotericin in severe systemic candidiasis and in other severe or long-standing infections

- By intravenous infusion or by mouth

Neonate 50 mg/kg every 12 hours

Child 1 month–18 years 50 mg/kg every 6 hours; extremely sensitive organisms, 25–37.5 mg/kg every 6 hours may be sufficient; treatment continued usually for not more than 7 days

Cryptococcal meningitis (adjunct to amphotericin, see Cryptococcosis, p. 304)

- By intravenous infusion or by mouth

Neonate 50 mg/kg every 12 hours

Child 1 month–18 years 25 mg/kg every 6 hours for 2 weeks

Administration for intravenous infusion, give over 20–40 minutes

Ancotil® (Meda) (PoM)

Intravenous infusion, flucytosine 10 mg/mL. Net price 250-mL infusion bottle = £30.33 (hosp. only)

Electrolytes Na⁺ 34.5 mmol/250-mL bottle

Note Flucytosine tablets may be available from 'special-order' manufacturers or specialist importing companies, see p. 840

GRISEOFULVIN

Cautions **interactions:** Appendix 1 (griseofulvin)

Skilled tasks May impair performance of skilled tasks; effects of alcohol enhanced

Contra-indications systemic lupus erythematosus (risk of exacerbation); acute porphyria (section 9.8.2)

Hepatic impairment avoid in severe liver disease

Pregnancy avoid (fetotoxicity and teratogenicity in *animals*); effective contraception required during and for at least 1 month after administration to women (**important:** effectiveness of oral contraceptives may be reduced, additional contraceptive precautions e.g. barrier method, required); also males should avoid fathering a child during and for at least 6 months after treatment

Breast-feeding avoid—no information available

Side-effects nausea, vomiting, diarrhoea, headache; also reported, abdominal pain, dyspepsia, hepatotoxicity, glossitis, taste disturbances, sleep disturbances, dizziness, fatigue, confusion, agitation, depression, impaired co-ordination and hearing, peripheral neuropathy, menstrual disturbances, renal failure, leucopenia, systemic lupus erythematosus, rash (including rarely erythema multiforme, toxic epidermal necrolysis), and photosensitivity

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Dermatophyte infections where topical therapy has failed or is inappropriate

- By mouth

Child 1 month–12 years 10 mg/kg (max. 500 mg) once daily or in divided doses; in severe infection dose may be doubled, reducing when response occurs

Child 12–18 years 500 mg once daily or in divided doses; in severe infection dose may be doubled, reducing when response occurs

Tinea capitis caused by *Trichophyton tonsurans*

- By mouth

Child 1 month–12 years 15–20 mg/kg (max. 1 g) once daily or in divided doses

Child 12–18 years 1 g once daily or in divided doses

Griseofulvin (Non-proprietary) (PoM)

Tablets, griseofulvin 125 mg, net price 100 = £35.39; 500 mg, 100 = £90.48. Label: 9, 21, counselling, skilled tasks

TERBINAFINE

Cautions psoriasis (risk of exacerbation); autoimmune disease (risk of lupus-erythematosus-like effect); monitor hepatic function before treatment and then every 4–6 weeks during treatment — discontinue if abnormalities in liver function tests; **interactions:** Appendix 1 (terbinafine)

Hepatic impairment manufacturer advises avoid—elimination reduced

Renal impairment use half normal dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m² and no suitable alternative available

Pregnancy manufacturer advises use only if benefit outweighs risk—no information available

Breast-feeding avoid—present in milk

Side-effects abdominal discomfort, anorexia, nausea, diarrhoea, dyspepsia, headache, arthralgia, myalgia, rash, urticaria; *less commonly* taste disturbance; *rarely* liver toxicity (including jaundice, cholestasis, and hepatitis)—discontinue treatment, dizziness, malaise, paraesthesia, hypoaesthesia; *very rarely* blood disorders (including neutropenia and thrombocytopenia),

lupus erythematosus-like effect, photosensitivity, alopecia, serious skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis)—discontinue treatment if progressive skin rash; also reported, pancreatitis, vasculitis, influenza-like symptoms, rhabdomyolysis, disturbances in smell, hearing disturbances, exacerbation of psoriasis

Licensed use not licensed for use in children

Indications and dose

Dermatophyte infections of the nails, ringworm infections (including tinea pedis, cruris, corporis, and capitis) where oral therapy appropriate (due to site, severity or extent)

• By mouth

Child over 1 year; body-weight 10–20 kg 62.5 mg once daily

Child body-weight 20–40 kg 125 mg once daily

Child body-weight over 40 kg 250 mg once daily

Note treatment usually for 4 weeks in tinea capitis, 2–6 weeks in tinea pedis, 2–4 weeks in tinea cruris, 4 weeks in tinea corporis, 6 weeks–3 months in nail infections (occasionally longer in toenail infections)

Fungal skin infections section 13.10.2

Terbinafine (Non-proprietary) PoM

Tablets, terbinafine (as hydrochloride) 250 mg, net price 14-tab pack = £1.47, 28-tab pack = £2.63. Label: 9

Lamisil® (Novartis) PoM

Tablets, off-white, scored, terbinafine (as hydrochloride) 250 mg, net price 14-tab pack = £21.30, 28-tab pack = £41.09. Label: 9

5.3 Antiviral drugs

- 5.3.1 HIV infection
- 5.3.2 Herpesvirus infections
- 5.3.3 Viral hepatitis
- 5.3.4 Influenza
- 5.3.5 Respiratory syncytial virus

The majority of virus infections resolve spontaneously in immunocompetent subjects. A number of specific treatments for viral infections are available, particularly for the immunocompromised. This section includes notes on herpes simplex and varicella-zoster, human immunodeficiency virus, cytomegalovirus, respiratory syncytial virus, viral hepatitis and influenza.

5.3.1 HIV infection

There is no cure for infection caused by the human immunodeficiency virus (HIV) but a number of drugs slow or halt disease progression. Drugs for HIV infection (antiretrovirals) may be associated with serious side-effects. Although antiretrovirals increase life expectancy considerably and decrease the risk of complications associated with premature ageing, mortality and morbidity remain slightly higher than in uninfected individuals.

The natural progression of HIV disease is different in children compared to adults; drug treatment should only be undertaken by specialists within a formal paediatric HIV clinical network. Guidelines and dose regimens are under constant review and for this reason some dose

recommendations have not been included in *BNF for Children*.

Further information on the management of children with HIV can be obtained from the Children's HIV Association (CHIVA) www.chiva.org.uk; and further information on antiretroviral use and toxicity can be obtained from the Paediatric European Network for Treatment of AIDS (PENTA) website www.pentatials.org.

Principles of treatment Treatment is aimed at suppressing viral replication for as long as possible; it should be started before the immune system is irreversibly damaged. The need for early drug treatment should, however, be balanced against the risk of toxicity. Commitment to treatment and strict adherence over many years are required; the regimen chosen should take into account convenience and the child's tolerance of treatment. The development of drug resistance is reduced by using a combination of drugs; such combinations should have synergistic or additive activity while ensuring that their toxicity is not additive. It is recommended that viral sensitivity to antiretroviral drugs is established before starting treatment or before switching drugs if the infection is not responding.

Initiation of treatment Treatment is started in all HIV infected children under 1 year of age regardless of clinical and immunological parameters. In children over 1 year of age, treatment is based on the child's age, CD4 cell count, viral load, and symptoms. The choice of antiviral treatment for children should take into account the method and frequency of administration, risk of side-effects, compatibility of drugs with food, palatability, and the appropriateness of the formulation. Initiating treatment with a combination of drugs ('highly active antiretroviral therapy' which includes 2 nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or a boosted protease inhibitor) is recommended. Abacavir and lamivudine are the nucleoside reverse transcriptase inhibitors of choice for initial therapy; however, zidovudine and lamivudine are used in children who are positive for the HLA-B*5701 allele. Nevirapine is the preferred non-nucleoside reverse transcriptase inhibitor in children under 3 years of age, but efavirenz is preferred in older children. Lopinavir with ritonavir is the preferred boosted protease inhibitor for initial therapy. The metabolism of many antiretrovirals varies in young children; it may therefore be necessary to adjust the dose according to the plasma-drug concentration. Children who require treatment for both HIV and chronic hepatitis B should receive antivirals that are active against both diseases (section 5.3.3).

Switching therapy Deterioration of the condition (including clinical, virological changes, and CD4 cell changes) may require a complete change of therapy. The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance, and the possibility of cross-resistance.

Pregnancy Treatment of HIV infection in pregnancy aims to reduce the risk of toxicity to the fetus (although information on the teratogenic potential of most antiretroviral drugs is limited), to minimise the viral load and disease progression in the mother, and to prevent transmission of infection to the neonate. **All treatment options require careful assessment by a specialist.** Combination antiretroviral therapy maximises the chance of preventing transmission and represents opti-

mal therapy for the mother. However, it may be associated with a greater risk of preterm delivery. Local protocols and national guidelines (www.bhiva.org) should be consulted for recommendations on treatment during pregnancy and the perinatal period. Pregnancies in HIV-positive women and babies born to them should be reported prospectively to the **National Study of HIV in Pregnancy and Childhood** at www.nshpc.ucl.ac.uk and to the **Antiretroviral Pregnancy Registry** at www.apregistry.com.

Mitochondrial dysfunction has been reported in infants exposed to nucleoside reverse transcriptase inhibitors in utero; the main effects include haematological, metabolic, and neurological disorders; all infants whose mothers received nucleoside reverse transcriptase inhibitors during pregnancy should be monitored for relevant signs or symptoms.

Breast-feeding Breast-feeding by HIV-positive mothers may cause HIV infection in the infant and should be avoided.

Neonates In order to prevent transmission of infection, neonates born to HIV-positive mothers should be given post-exposure prophylaxis as soon as possible after birth, but starting no later than 72 hours after birth. Zidovudine alone should be given to neonates whose mothers had a viral load less than 50 HIV RNA copies/mL between 36 weeks' gestation and delivery, or whose mothers underwent caesarean section while taking zidovudine monotherapy. Combination antiretroviral therapy should be given to neonates whose mothers had a viral load over 50 HIV RNA copies/mL at delivery or whose mothers are found to be HIV positive after delivery. Prophylaxis is continued for 4 weeks.

Post-exposure prophylaxis Children exposed to HIV infection through needlestick injury or by another route should be sent immediately to an accident and emergency department for post-exposure prophylaxis [unlicensed indication]. Antiretrovirals for prophylaxis are chosen on the basis of efficacy and potential for toxicity. Recommendations have been developed by the Children's HIV Association, www.chiva.org.uk.

Drugs used for HIV infection Zidovudine, a nucleoside reverse transcriptase inhibitor (or 'nucleoside analogue'), was the first anti-HIV drug to be introduced. Other nucleoside reverse transcriptase inhibitors include **abacavir**, **didanosine**, **emtricitabine**, **lamivudine**, **stavudine**, and **tenofovir**. There are concerns about renal toxicity and effects on bone mineralisation when tenofovir is used in prepubertal children.

The protease inhibitors include **atazanavir**, **darunavir**, **fosamprenavir** (a pro-drug of amprenavir), **indinavir**, **lopinavir**, **ritonavir**, and **tipranavir**. Indinavir is no longer recommended because it is associated with nephrolithiasis. Ritonavir in low doses boosts the activity of atazanavir, darunavir, fosamprenavir, lopinavir, and tipranavir increasing the persistence of plasma concentrations of these drugs; at such a low dose, ritonavir has no intrinsic antiviral activity. A combination of lopinavir with low-dose ritonavir is available for use in children. The protease inhibitors are metabolised by cytochrome P450 enzyme systems and therefore have a significant potential for drug interactions. Protease inhibitors are associated with lipodystrophy and metabolic effects (see below).

The non-nucleoside reverse transcriptase inhibitors **efavirenz**, **etravirine**, and **nevirapine** are active against

the subtype HIV-1 but not HIV-2, a subtype that is rare in the UK. These drugs may interact with a number of drugs metabolised in the liver. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and rarely fatal hepatitis. Rash is also associated with efavirenz and etravirine but it is usually milder. Psychiatric or CNS disturbances are common with efavirenz. CNS disturbances are often self-limiting and can be reduced by taking the dose at bedtime (especially in the first 2–4 weeks of treatment). Efavirenz has also been associated with an increased plasma cholesterol concentration. Etravirine is used in regimens containing a boosted protease inhibitor for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

Enfuvirtide, which inhibits the fusion of HIV to the host cell, is licensed for managing infection that has failed to respond to a regimen of other antiretroviral drugs. Enfuvirtide should be combined with other potentially active antiretroviral drugs; it is given by subcutaneous injection.

Maraviroc is an antagonist of the CCR5 chemokine receptor. It is used in patients exclusively infected with CCR5-tropic HIV.

Dolutegravir and **raltegravir** are inhibitors of HIV integrase. They are used for the treatment of HIV infection when non-nucleoside reverse transcriptase inhibitors or protease inhibitors cannot be used because of intolerance, drug interactions, or resistance.

Immune reconstitution syndrome Improvement in immune function as a result of antiretroviral treatment may provoke a marked inflammatory reaction against residual opportunistic organisms; these reactions may occur within the first few weeks or months of initiating treatment. Autoimmune disorders (such as Graves' disease) have also been reported many months after initiation of treatment.

Lipodystrophy syndrome Metabolic effects associated with antiretroviral treatment include *fat redistribution*, *insulin resistance*, and *dyslipidaemia*; collectively these have been termed *lipodystrophy syndrome*. Children should be encouraged to lead a healthy lifestyle that reduces their long-term cardiovascular risk. Plasma lipids and blood glucose should be measured before starting antiretroviral therapy, after 3–6 months of treatment, and then at least annually. Insulin resistance and hyperglycaemia occur only rarely in children.

Fat redistribution (with loss of subcutaneous fat, increased abdominal fat, 'buffalo hump' and breast enlargement) is associated with regimens containing protease inhibitors and nucleoside reverse transcriptase inhibitors. Stavudine, and to a lesser extent zidovudine, are associated with a higher risk of lipodystrophy and should be used only if alternative regimens are not suitable.

Dyslipidaemia is associated with antiretroviral treatment, particularly with protease inhibitors; in children, hypercholesterolaemia appears to be more common than hypertriglyceridaemia. Protease inhibitors and some nucleoside reverse transcriptase inhibitors are associated with insulin resistance and hyperglycaemia, but they occur rarely in children. Of the protease inhibitors, atazanavir and darunavir are less likely to cause dyslipidaemia, while atazanavir is less likely to impair glucose tolerance.

Osteonecrosis Osteonecrosis has been reported in children with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.

Nucleoside reverse transcriptase inhibitors

Cautions

Lactic acidosis Life-threatening lactic acidosis associated with hepatomegaly and hepatic steatosis has been reported with nucleoside reverse transcriptase inhibitors. They should be used with caution in children with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver-enzyme abnormalities and with other risk factors for liver disease and hepatic steatosis. Treatment with the nucleoside reverse transcriptase inhibitor should be **discontinued** in case of symptomatic hyperlactataemia, lactic acidosis, progressive hepatomegaly or rapid deterioration of liver function. Stavudine, especially with didanosine, is associated with a higher risk of lactic acidosis and should be used only if alternative regimens are not suitable.

Hepatic impairment Nucleoside reverse transcriptase inhibitors should be used with caution in children with hepatic impairment (greater risk of hepatic side-effects, see also Lactic Acidosis above). However, some nucleoside reverse transcriptase inhibitors are used in children who also have chronic hepatitis B.

Pregnancy See p. 313

Breast-feeding See p. 314

Side-effects Side-effects of the nucleoside reverse transcriptase inhibitors include gastro-intestinal disturbances (such as nausea, vomiting, abdominal pain, flatulence and diarrhoea), anorexia, pancreatitis, liver damage (see also Lactic Acidosis, above), dyspnoea, cough, headache, insomnia, dizziness, fatigue, blood disorders (including anaemia, neutropenia, and thrombocytopenia), myalgia, arthralgia, rash, urticaria, and fever. See notes above for Lipodystrophy Syndrome (p. 314) and Osteonecrosis (above).

ABACAVIR

Cautions see notes above; also test for HLA-B*5701 allele before treatment (or if re-starting treatment and HLA-B*5701 status not known)—increased risk of hypersensitivity reaction in presence of HLA-B*5701 allele; **interactions:** Appendix 1 (abacavir)

Hypersensitivity reactions Life-threatening hypersensitivity reactions reported—characterised by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, dyspnoea, cough, lethargy, malaise, headache, and myalgia; less frequently mouth ulceration, oedema, hypotension, sore throat, acute respiratory distress syndrome, anaphylaxis, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and renal failure; rarely myolysis; laboratory abnormalities may include raised liver function tests (see Lactic Acidosis above) and creatine kinase; symptoms usually appear in the first 6 weeks, but may occur at any time; monitor for symptoms every 2 weeks for 2 months; discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction); discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible—if rechallenge necessary it must be carried out in hospital setting; if abacavir is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause and rechallenge only if

medical assistance is readily available; care needed with concomitant use of drugs which cause skin toxicity
Counselling Children and carers should be told the importance of regular dosing (intermittent therapy may increase the risk of sensitisation), how to recognise signs of hypersensitivity, and advised to seek immediate medical attention if symptoms develop or before re-starting treatment; children or their carers should be advised to keep Alert Card with them at all times

Hepatic impairment see notes above; also avoid in moderate impairment unless essential; avoid in severe impairment

Renal impairment manufacturer advises avoid in end-stage renal disease; avoid *Kivexa*® or *Trizivir*® if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²

Pregnancy see p. 313

Breast-feeding see p. 314

Side-effects see notes above; also hypersensitivity reactions (see above); *very rarely* Stevens-Johnson syndrome and toxic epidermal necrolysis; rash and gastro-intestinal disturbances more common in children

Licensed use *Trizivir*® not licensed for use in children
Indications and dose

HIV infection in combination with other anti-retroviral drugs

• By mouth

Child 3 months–12 years 8 mg/kg (max. 300 mg) twice daily *or* 16 mg/kg (max. 600 mg) once daily *or*

Body-weight 14–21 kg 150 mg twice daily *or* 300 mg once daily

Body-weight 21–30 kg 150 mg in the morning and 300 mg in the evening *or* 450 mg once daily

Body-weight over 30 kg 300 mg twice daily *or* 600 mg once daily

Child 12–18 years 300 mg twice daily *or* 600 mg once daily

Ziagen® (ViiV) (PoM)

Tablets, yellow, f/c, scored, abacavir (as sulfate) 300 mg, net price 60-tab pack = £177.60. Counselling, hypersensitivity reactions

Oral solution, sugar-free, banana and strawberry flavoured, abacavir (as sulfate) 20 mg/mL, net price 240-mL = £47.36. Counselling, hypersensitivity reactions

Excipients include propylene glycol

▲ With lamivudine

For cautions, contra-indications, side-effects, and other prescribing information see under individual drugs

Kivexa® (ViiV) (PoM)

Tablets, orange, f/c, abacavir (as sulfate) 600 mg, lamivudine 300 mg, net price 30-tab pack = £299.41. Counselling, hypersensitivity reactions

Dose

HIV infection in combination with other antiretroviral drugs

• By mouth

Child 12–18 years and body-weight over 40 kg 1 tablet once daily

With lamivudine and zidovudine

Note Use only if child is stabilised (for 6–8 weeks) on the individual components in the same proportions. For **cautions**, **contra-indications**, **side-effects**, and other prescribing information see under individual drugs

Trizivir® (ViiV) (PoM)

Tablets, blue-green, f/c, abacavir (as sulfate) 300 mg, lamivudine 150 mg, zidovudine 300 mg, net price 60-tab pack = £432.70. Counselling, hypersensitivity reactions

Dose

HIV infection

• By mouth

Child body-weight over 30 kg 1 tablet twice daily

DIDANOSINE

(ddl, DDI)

Cautions see notes above; also history of pancreatitis (preferably avoid, otherwise extreme caution, see also below); peripheral neuropathy or hyperuricaemia (see under Side-effects); ophthalmological examination (including visual acuity, colour vision, and dilated fundus examination) recommended annually or if visual changes occur; **interactions**: Appendix 1 (didanosine)

Pancreatitis If symptoms of pancreatitis develop or if serum lipase is raised and pancreatitis is confirmed, discontinue treatment. Whenever possible avoid concomitant treatment with other drugs known to cause pancreatic toxicity (e.g. intravenous pentamidine isetionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if triglycerides elevated

Hepatic impairment see notes above

Renal impairment reduce dose if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²; consult product literature

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 314

Side-effects see notes above; also pancreatitis (less common in children, see also under Cautions), liver failure, non-cirrhotic portal hypertension, anaphylactic reactions, peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops), diabetes mellitus, hypoglycaemia, acute renal failure, rhabdomyolysis, dry eyes, retinal and optic nerve changes, dry mouth, parotid gland enlargement, sialadenitis, alopecia, hyperuricaemia (suspend if raised significantly)

Licensed use tablets not licensed for use in children under 3 months; EC capsules not licensed for use in children under 6 years

Indications and dose

HIV infection in combination with other antiretroviral drugs

• By mouth

Child 1–8 months 50–100 mg/m² twice daily

Child 8 months–18 years 180–240 mg/m² once daily; usual dose 200 mg/m² once daily; max. 400 mg daily

Videx® (Bristol-Myers Squibb) (PoM)

Tablets, with calcium and magnesium antacids, didanosine 25 mg, net price 60-tab pack = £25.06.

Label: 23, counselling, administration, see below

Excipients include aspartame equivalent to phenylalanine 36.5 mg per tablet (section 9.4.1)

Note Antacids in formulation may affect absorption of other drugs—see **interactions**: Appendix 1 (antacids)

Administration to ensure sufficient antacid, each dose to be taken as at least 2 tablets (**child** under 1 year 1 tablet) chewed thoroughly, crushed or dispersed in water; clear apple juice may be added for flavouring; tablets to be taken 2 hours after lopinavir with ritonavir capsules and oral solution or atazanavir with ritonavir

Videx® EC capsules, enclosing e/c granules, didanosine 125 mg, net price 30-cap pack = £48.18; 200 mg, 30-cap pack = £77.09; 250 mg, 30-cap pack = £96.37; 400 mg, 30-cap pack = £154.19. **Label**: 25, counselling, administration, see below

Administration capsules should be swallowed whole and taken at least 2 hours before or 2 hours after food

EMTRICITABINE

(FTC)

Cautions see notes above; also on discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis); **interactions**: Appendix 1 (emtricitabine)

Hepatic impairment see notes above and Cautions above

Renal impairment reduce dose or increase dosage interval if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²; consult product literature

Pregnancy see p. 313

Breast-feeding see p. 314

Side-effects see notes above; also abnormal dreams, pruritus, and hyperpigmentation

Indications and dose

See Preparations

Emtriva® (Gilead) (PoM)

Capsules, white/blue, emtricitabine 200 mg, net price 30-cap pack = £163.50

Dose

HIV infection in combination with other antiretroviral drugs

• By mouth

Child body-weight over 33 kg 200 mg once daily

Oral solution, orange, emtricitabine 10 mg/mL, net price 170-mL pack (candy-flavoured) = £46.50

Electrolytes Na⁺ 460 micromol/mL

Dose

HIV infection in combination with other antiretroviral drugs

• By mouth

Child 4 months–18 years

Body-weight under 33 kg 6 mg/kg once daily

Body-weight over 33 kg 240 mg once daily

Note 240 mg oral solution = 200 mg capsule; where appropriate the capsule may be used instead of the oral solution

Missed dose If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time

With tenofovir

See under Tenofovir

With efavirenz and tenofovir

See under Tenofovir

LAMIVUDINE (3TC)

Cautions see notes above; **interactions:** Appendix 1 (lamivudine)

Chronic hepatitis B Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine. When treating chronic hepatitis B with lamivudine, monitor liver function tests every 3 months, and viral markers of hepatitis B every 3–6 months, more frequently in patients with advanced liver disease or following transplantation (monitoring to continue for at least 1 year after discontinuation)

Hepatic impairment see notes above and Cautions above

Renal impairment reduce dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²; consult product literature

Pregnancy see p. 313

Breast-feeding can be used with caution in women infected with chronic hepatitis B alone, providing that adequate measures are taken to prevent hepatitis B infection in infants; for women infected with HIV, see p. 314

Side-effects see notes above; also peripheral neuropathy, muscle disorders including rhabdomyolysis, nasal symptoms, alopecia

Licensed use *Epivir*[®] not licensed for use in children under 3 months; *Zeffix*[®] not licensed for use in children

Indications and dose See Preparations

Epivir[®] (ViiV) (PoM)

Tablets, f/c lamivudine 150 mg (scored, white), net price 60-tab pack = £121.82; 300 mg (grey), 30-tab pack = £133.89

Oral solution, banana- and strawberry-flavoured, lamivudine 50 mg/5 mL, net price 240-mL pack = £33.16

Excipients include sucrose 1 g/5 mL

Dose

HIV infection in combination with other antiretroviral drugs

• By mouth

Child 1–3 months 4 mg/kg twice daily

Child 3 months–12 years 4 mg/kg (max. 150 mg) twice daily or 8 mg/kg (max. 300 mg) once daily

or

Body-weight 14–21 kg 75 mg twice daily or 150 mg once daily

Body-weight 21–30 kg 75 mg in the morning and 150 mg in the evening or 225 mg once daily

Body-weight over 30 kg 150 mg twice daily or 300 mg once daily

Child 12–18 years 150 mg twice daily or 300 mg once daily

Zeffix[®] (ViiV) (PoM)

Tablets, brown, f/c, lamivudine 100 mg, net price 28-tab pack = £78.09

Dose

Chronic hepatitis B infection *either* with compensated liver disease (with evidence of viral replication and histology of active liver inflammation or fibrosis) when first-line treatments cannot be used, or (in combination with another antiviral drug without cross-resistance to lamivudine) with decompensated liver disease

• By mouth

Child 2–12 years 3 mg/kg (max. 100 mg) once daily

Child 12–18 years 100 mg once daily

Note Children receiving lamivudine for concomitant HIV infection should continue to receive lamivudine in a dose appropriate for HIV infection

■ With abacavir

See under Abacavir

■ With zidovudine

See under Zidovudine

■ With abacavir and zidovudine

See under Abacavir

STAVUDINE (d4T)

Cautions see notes above; also history of peripheral neuropathy, excessive alcohol intake, concomitant use of isoniazid—risk of peripheral neuropathy (see under Side-effects); history of pancreatitis or concomitant use with other drugs associated with pancreatitis; **interactions:** Appendix 1 (stavudine)

Hepatic impairment see notes above

Renal impairment risk of peripheral neuropathy; reduce dose to 50% if estimated glomerular filtration rate 25–50 mL/minute/1.73 m²; reduce dose to 25% if estimated glomerular filtration rate less than 25 mL/minute/1.73 m²

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 314

Side-effects see notes above; also peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops), abnormal dreams, cognitive dysfunction, drowsiness, depression, pruritus; *less commonly* anxiety, gynaecomastia

Licensed use capsules not licensed for use in children under 3 months

Indications and dose

HIV infection in combination with other antiretroviral drugs when no suitable alternative available and when prescribed for shortest period possible

• By mouth

Child 1 month–18 years

Body-weight under 30 kg 1 mg/kg twice daily, preferably at least 1 hour before food

Body-weight 30–60 kg 30 mg twice daily, preferably at least 1 hour before food

Body-weight over 60 kg 40 mg twice daily, preferably at least 1 hour before food

Zerit[®] (Bristol-Myers Squibb) (PoM) 

Capsules, stavudine 20 mg (brown), net price 56-cap pack = £139.46; 30 mg (light orange/dark orange), 56-cap pack = £146.25; 40 mg (dark orange), 56-cap pack = £150.66 (all hosp. only)

Oral solution, cherry-flavoured, stavudine for reconstitution with water, 1 mg/mL, net price 200 mL = £22.94

TENOFOVIR DISOPROXIL

Cautions see notes above; also test renal function and serum phosphate before treatment, then every 4 weeks (more frequently if at increased risk of renal impairment) for 1 year and then every 3 months, interrupt treatment if renal function deteriorates or serum phosphate decreases; concomitant or recent use of nephrotoxic drugs; **interactions:** Appendix 1 (tenofovir)

Chronic hepatitis B When treating chronic hepatitis B with tenofovir, monitor liver function tests every 3 months and

viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation)

Hepatic impairment see notes above and Cautions above; manufacturer of *Atripla*® advises caution in mild impairment; avoid *Atripla*® in moderate to severe impairment

Renal impairment manufacturer advises avoid—no information available

Pregnancy see p. 313

Breast-feeding see p. 314

Side-effects see notes above; also hypophosphataemia; rarely renal failure, proximal renal tubulopathy, nephrogenic diabetes insipidus; also reported reduced bone density

Indications and dose

HIV infection in combination with other anti-retroviral drugs when first-line nucleoside reverse transcriptase inhibitors cannot be used because of resistance or contra-indications

- By mouth
- **Child 2–18 years** 6.5 mg/kg (max. 245 mg) once daily
- or
- Child 6–18 years**
- Body-weight 17–22 kg** 123 mg once daily
- Body-weight 22–28 kg** 163 mg once daily
- Body-weight 28–35 kg** 204 mg once daily
- Body-weight over 35 kg** 245 mg once daily

Chronic hepatitis B infection with compensated liver disease (with evidence of viral replication, and histology of active liver inflammation or fibrosis)

- By mouth
- Child 12–18 years, body-weight over 35 kg** 245 mg once daily

Missed dose If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time

Viread® (Gilead) (PoM)

Tablets, f/c, tenofovir disoproxil (as fumarate) 123 mg (white), net price 30-tab pack = £102.60; 163 mg (white), 30-tab pack = £135.98; 204 mg (white), 30-tab pack = £170.19; 245 mg (blue), 30-tab pack = £240.46. Label: 21

Granules, sugar-free, tenofovir disoproxil (as fumarate) 33 mg/g, net price 60 g (with 1-g scoop) = £54.50. Label: 21, counselling, administration

Note 7.5 scoops of granules contains approx. 245 mg tenofovir disoproxil (as fumarate)

Administration Mix 1 scoop of granules with 1 tablespoon of soft food (e.g. yoghurt, apple sauce) and take immediately without chewing. Do not mix granules with liquids

With emtricitabine

For cautions, contra-indications, side-effects, and other prescribing information see under individual drugs

Truvada® (Gilead) (PoM)

Tablets, blue, f/c, tenofovir disoproxil (as fumarate) 245 mg, emtricitabine 200 mg, net price 30-tab pack = £418.50. Label: 21, Counselling, administration Children with swallowing difficulties may disperse tablet in half a glass of water, orange juice, or grape juice (but bitter taste)

With efavirenz and emtricitabine

For cautions, contra-indications, side-effects, and other prescribing information see under individual drugs

Atripla® (Gilead) (PoM)

Tablets, pink, f/c, efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil (as fumarate) 245 mg, net price 30-tab pack = £626.90. Label: 23, 25

ZIDOVUDINE

(Azidothymidine, AZT)

Note The abbreviation AZT which is sometimes used for zidovudine has also been used for another drug

Cautions see notes above; also haematological toxicity particularly with high dose and advanced disease—monitor full blood count after 4 weeks of treatment, then every 3 months; vitamin B₁₂ deficiency (increased risk of neutropenia); if anaemia or myelosuppression occur, reduce dose or interrupt treatment according to product literature, or consider other treatment; **interactions**: Appendix 1 (zidovudine)

Contra-indications abnormally low neutrophil count or haemoglobin concentration (consult product literature); neonates with hyperbilirubinaemia requiring treatment other than phototherapy, or with raised transaminase (consult product literature); acute porphyria (section 9.8.2)

Hepatic impairment see notes above; also accumulation may occur

Renal impairment reduce dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²—consult product literature; avoid *Combivir*® (or non-proprietary equivalents) if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²

Pregnancy see p. 313

Breast-feeding see p. 314

Side-effects see notes above; also anaemia (may require transfusion), taste disturbance, chest pain, influenza-like symptoms, paraesthesia, neuropathy, convulsions, dizziness, drowsiness, anxiety, depression, loss of mental acuity, myopathy, gynaecomastia, urinary frequency, sweating, pruritus, pigmentation of nails, skin and oral mucosa

Indications and dose

HIV infection in combination with other anti-retroviral drugs

- By mouth
- Child 1 month–18 years** 180 mg/m² (max. 300 mg) twice daily
- or
- Body-weight 4–9 kg** 12 mg/kg twice daily
- Body-weight 9–30 kg** 9 mg/kg twice daily
- Body-weight over 30 kg** 250–300 mg twice daily
- or
- Body-weight 8–14 kg** 100 mg twice daily
- Body-weight 14–21 kg** 100 mg in the morning and 200 mg in the evening
- Body-weight 21–28 kg** 200 mg twice daily
- Body-weight 28–30 kg** 200–250 mg twice daily

- By intravenous infusion over 1 hour in children temporarily unable to take zidovudine by mouth

Child 3 months–12 years 60–80 mg/m² every 6 hours (approximating to 9–12 mg/kg twice daily by mouth) usually for not more than 2 weeks

Child 12–18 years 0.8–1 mg/kg every 4 hours (approximating to 1.2–1.5 mg/kg every 4 hours by mouth) usually for not more than 2 weeks

Prevention of maternal-fetal HIV transmission

seek specialist advice (combination therapy preferred)

Administration for intermittent intravenous infusion, dilute to a concentration of 2 mg/mL or 4 mg/mL with Glucose 5% and give over 1 hour.

For administration by mouth, *Combivir*® tablets may be crushed and mixed with semi-solid food or liquid just before administration

Zidovudine (Non-proprietary) (PoM)

Capsules, zidovudine 100 mg, net price 60-cap pack = £50.17; 250 mg, 60-cap pack = £125.44

Retrovir® (ViiV) (PoM)

Capsules, zidovudine 100 mg (white), net price 100-cap pack = £88.86; 250 mg (blue/white), 40-cap pack = £88.86

Oral solution, sugar-free, strawberry-flavoured, zidovudine 50 mg/5 mL, net price 200-mL pack with 10-mL oral syringe = £17.78

Injection, zidovudine 10 mg/mL. For dilution and use as an intravenous infusion. Net price 20-mL vial = £8.92

■ With lamivudine

For cautions, contra-indications, side-effects, and other prescribing information see under individual drugs

Zidovudine and lamivudine (Non-proprietary) (PoM)

Tablets, f/c, scored, zidovudine 300 mg, lamivudine 150 mg, net price 60-tab pack = £210.08

Dose

HIV infection in combination with other antiretrovirals

- By mouth
 - Child body-weight 14–21 kg** half a tablet twice daily
 - Child body-weight 21–30 kg** half a tablet in the morning and one tablet in the evening
 - Child body-weight over 30 kg** one tablet twice daily

Combivir® (ViiV) (PoM)

Tablets, f/c, zidovudine 300 mg, lamivudine 150 mg, net price 60-tab pack = £255.10

Dose

HIV infection in combination with other antiretrovirals

- By mouth
 - Child body-weight 14–21 kg** half a tablet twice daily
 - Child body-weight 21–30 kg** half a tablet in the morning and one tablet in the evening
 - Child body-weight over 30 kg** one tablet twice daily

■ With abacavir and lamivudine

See under Abacavir

Protease inhibitors

Cautions Protease inhibitors should be used with caution in diabetes (see also Lipodystrophy Syndrome,

p. 314). Caution is also needed in children with haemophilia who may be at increased risk of bleeding.

Contra-indications Protease inhibitors should not be given to patients with acute porphyria (but see section 9.8.2).

Hepatic impairment Protease inhibitors should be used with caution in children with chronic hepatitis B or C (increased risk of hepatic side-effects).

Pregnancy See p. 313

Breast-feeding See p. 314

Side-effects Side-effects of the protease inhibitors include gastro-intestinal disturbances (including diarrhoea, nausea, vomiting, abdominal pain, flatulence), anorexia, hepatic dysfunction, pancreatitis; blood disorders including anaemia, neutropenia, and thrombocytopenia; sleep disturbances, fatigue, headache, dizziness, paraesthesia, myalgia, myositis, rhabdomyolysis; taste disturbances; rash, pruritus, Stevens-Johnson syndrome, hypersensitivity reactions including anaphylaxis; see also Lipodystrophy Syndrome (p. 314) and Osteonecrosis (p. 315).

ATAZANAVIR

Cautions see notes above; concomitant use with drugs that prolong PR interval; cardiac conduction disorders; predisposition to QT interval prolongation (including electrolyte disturbances, concomitant use of drugs that prolong QT interval); **interactions:** Appendix 1 (atazanavir)

Rash Mild to moderate rash occurs commonly, usually within the first 3 weeks of therapy. Severe rash occurs less frequently and may be accompanied by systemic symptoms. Discontinue if severe rash develops

Contra-indications see notes above

Hepatic impairment see notes above; also use with caution in mild impairment; avoid in moderate to severe impairment

Pregnancy see p. 313; monitor viral load and plasma-atazanavir concentration during third trimester; theoretical risk of hyperbilirubinaemia in neonate if used at term

Breast-feeding see p. 314

Side-effects see notes above; also AV block; less commonly mouth ulcers, dry mouth, cholelithiasis, hypertension, syncope, chest pain, torsades de pointes, dyspnoea, peripheral neuropathy, abnormal dreams, amnesia, disorientation, depression, anxiety, weight changes, increased appetite, gynaecomastia, nephrolithiasis, urinary frequency, haematuria, proteinuria, arthralgia, alopecia; rarely cholecystitis, hepatosplenomegaly, oedema, palpitation, abnormal gait

Indications and dose

HIV infection in combination with other anti-retroviral drugs

- By mouth
 - With low-dose ritonavir
 - Child 6–18 years**
 - Body-weight 15–20 kg** 150 mg once daily
 - Body-weight 20–40 kg** 200 mg once daily
 - Body-weight over 40 kg** 300 mg once daily

Reyataz® (Bristol-Myers Squibb) ▼ (PoM)

Capsules, atazanavir (as sulfate) 150 mg (dark blue/light blue), net price 60-cap pack = £303.38; 200 mg (dark blue), 60-cap pack = £303.38; 300 mg (red/blue), 30-cap pack = £303.38. Label: 5, 21

DARUNAVIR

Cautions see notes above; also sulfonamide sensitivity; monitor liver function before and during treatment; **interactions**: Appendix 1 (darunavir)

Rash Mild to moderate rash occurs commonly, usually within the first 4 weeks of therapy and resolves without stopping treatment. Severe skin rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis) occurs less frequently and may be accompanied by fever, malaise, arthralgia, myalgia, oral lesions, conjunctivitis, hepatitis, or eosinophilia; treatment should be stopped if severe rash develops

Contra-indications see notes above

Hepatic impairment see notes above; also manufacturer advises caution in mild to moderate impairment; avoid in severe impairment—no information available

Pregnancy manufacturer advises use only if potential benefit outweighs risk; if required, use the twice daily dose regimen; see also p. 313

Breast-feeding see p. 314

Side-effects see notes above; also peripheral neuropathy; *less commonly* myocardial infarction, chest pain, QT interval prolongation, tachycardia, hypertension, flushing, peripheral oedema, dyspnoea, cough, anxiety, memory impairment, depression, abnormal dreams, increased appetite, weight changes, pyrexia, hypothyroidism, osteoporosis, gynaecomastia, erectile dysfunction, reduced libido, dysuria, polyuria, nephrolithiasis, renal failure, arthralgia, dry eyes, conjunctival hyperaemia, throat irritation, dry mouth, stomatitis, nail discoloration, acne, eczema, increased sweating, alopecia; *rarely* haematemesis, syncope, bradycardia, palpitation, confusion, convulsions, visual disturbances, rhinorrhoea, seborrhoeic dermatitis

Indications and dose

In combination with other antiretroviral drugs, for HIV infection in children previously treated with antiretrovirals

- By mouth

With low-dose ritonavir

Child 3–18 years

Body-weight 15–30 kg 375 mg twice daily

Body-weight 30–40 kg 450 mg twice daily

Body-weight over 40 kg 600 mg twice daily *or* **child 12–18 years** (if no resistance to darunavir, if plasma HIV-RNA concentration less than 100 000 copies/mL, and if CD4 cell count greater than 100 cells $\times 10^6$ /litre), 800 mg once daily

In combination with other antiretroviral drugs, for HIV infection not previously treated with antiretroviral therapy

- By mouth

With low-dose ritonavir

Child 12–18 years and body-weight over 40 kg 800 mg once daily

Missed dose If a dose is more than 6 hours late on the twice daily regimen (or more than 12 hours late on the once daily regimen), the missed dose should not be taken and the next dose should be taken at the normal time

Prezista® (Janssen) (PoM)

Tablets, f/c, darunavir (as ethanolate) 75 mg (white), net price 480-tab pack = £446.70; 150 mg (white), 240-tab pack = £446.70; 400 mg (light orange), 60-tab pack = £297.80; 600 mg (orange), 60-tab pack = £446.70; 800 mg (red), 30-tab pack = £297.80. Label: 21

Oral suspension, sugar-free, strawberry-flavoured, darunavir (as ethanolate) 100 mg/mL, net price 200-mL = £248.17. Label: 21

FOSAMPRENAVIR

Note Fosamprenavir is a pro-drug of amprenavir

Cautions see notes above; **interactions**: Appendix 1 (fosamprenavir)

Rash Rash may occur, usually in the second week of therapy; discontinue permanently if severe rash with systemic or allergic symptoms or, mucosal involvement; if rash mild or moderate, may continue without interruption—usually resolves within 2 weeks and may respond to antihistamines

Contra-indications see notes above

Hepatic impairment see notes above; also manufacturer advises caution in mild impairment; reduce dose in moderate to severe impairment

Pregnancy toxicity in *animal studies*; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 314

Side-effects see notes above; also reported, rash including rarely Stevens-Johnson syndrome (see also Rash above)

Indications and dose

HIV infection in combination with other antiretroviral drugs

- By mouth

With low-dose ritonavir

Child 6–18 years

Body-weight 25–39 kg 18 mg/kg (max. 700 mg) twice daily

Body-weight over 39 kg 700 mg twice daily

Note 700 mg fosamprenavir is equivalent to approx. 600 mg amprenavir

Telzir® (ViiV) (PoM)

Tablets, f/c, pink, fosamprenavir (as calcium) 700 mg, net price 60-tab pack = £220.13

Oral suspension, fosamprenavir (as calcium) 50 mg/mL, net price 225-mL pack (grape-bubblegum and peppermint-flavoured) (with 10-mL oral syringe) = £58.70. Counselling, administration

Excipients include propylene glycol

Administration In children, oral suspension should be taken with food

LOPINAVIR WITH RITONAVIR

Cautions see notes above; concomitant use with drugs that prolong QT or PR interval; cardiac conduction disorders, structural heart disease; pancreatitis (see below); monitor liver function before and during treatment; **interactions**: Appendix 1 (lopinavir, ritonavir)

Pancreatitis Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

Contra-indications see notes above

Hepatic impairment see notes above; also avoid oral solution—high propylene glycol content; manufacturer advises avoid tablets in severe impairment

Renal impairment avoid oral solution due to high propylene glycol content

Pregnancy avoid oral solution due to high propylene glycol content; use tablets only if potential benefit outweighs risk (toxicity in *animal studies*); for tablets see also p. 313

Breast-feeding see p. 314

Side-effects see notes and Cautions above; also colitis, weight changes, hypertension, anxiety, neuropathy, sexual dysfunction, amenorrhoea, menorrhagia, arthralgia, night sweats; *less commonly* gastro-intestinal ulcer, rectal bleeding, dry mouth, stomatitis, atherosclerosis, AV block, cerebrovascular accident, deep vein thrombosis, abnormal dreams, convulsions, tremor, nephritis, haematuria, visual disturbances, tinnitus, alopecia

Indications and dose

See Preparations

Kaletra® (AbbVie) (PoM)

Tablets, pale yellow, f/c, lopinavir 100 mg, ritonavir 25 mg, net price 60-tab pack = £76.85. Label: 25

Dose

HIV infection in combination with other antiretroviral drugs

• By mouth

Child 2–18 years with body-weight under 40 kg

Body surface area 0.5–0.9 m² 2 tablets twice daily

Body surface area 0.9–1.4 m² 3 tablets twice daily

Tablets, yellow, f/c, lopinavir 200 mg, ritonavir 50 mg, net price 120-tab pack = £285.41. Label: 25

Dose

HIV infection in combination with other antiretroviral drugs

• By mouth

Child 2–18 years with body surface area greater than 1.4 m² or body-weight 40 kg and over 2 tablets twice daily

Oral solution, lopinavir 400 mg, ritonavir 100 mg/5 mL, net price 5 × 60-mL packs = £307.39. Label: 21

Excipients include propylene glycol 153 mg/mL (see Excipients, p. 2), alcohol 42%

Dose

HIV infection in combination with other antiretroviral drugs

• By mouth

Child 2–18 years 2.9 mL/m² (max. 5 mL) twice daily with food

Counselling Oral solution tastes bitter

RITONAVIR

Cautions see notes above; concomitant use with drugs that prolong PR interval; cardiac conduction disorders, structural heart disease; pancreatitis (see below); **interactions:** Appendix 1 (ritonavir)

Pancreatitis Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

Contra-indications see notes above

Hepatic impairment see notes above; also avoid in decompensated liver disease; in severe impairment without decompensation, use 'booster' doses with caution (avoid treatment doses)

Pregnancy only use low-dose booster to increase the effect of other protease inhibitors; see also p. 313

Breast-feeding see p. 314

Side-effects see notes and Cautions above; also gastro-intestinal haemorrhage, blood pressure changes, oedema, syncope, flushing, cough, pharyngitis, anxiety, confusion, seizures, peripheral neuropathy, fever, decreased blood thyroxine concentration, menorrhagia, renal impairment, arthralgia, blurred vision, mouth ulcers, acne; *less commonly* myocardial infarction, electrolyte disturbances; *rarely* toxic epidermal necrolysis

Indications and dose

Low-dose ritonavir to increase the effect of atazanavir

• By mouth

Child 6–18 years

Body-weight 15–20 kg 80–100 mg once daily

Body-weight over 20 kg 100 mg once daily

Low-dose ritonavir to increase the effect of darunavir

• By mouth

Child 3–18 years

Body-weight 15–30 kg 50 mg twice daily

Body-weight 30–40 kg 60 mg twice daily

Body-weight over 40 kg 100 mg twice daily

(100 mg once daily if using once daily darunavir regimen in **child 12–18 years**)

Low-dose ritonavir to increase the effect of fosamprenavir

• By mouth

Child 6–18 years

Body-weight 25–33 kg 3 mg/kg twice daily

Body-weight over 33 kg 100 mg twice daily

Low-dose ritonavir to increase the effect of tipranavir

• By mouth

Child 2–12 years 150 mg/m² (max. 200 mg) twice daily

Child 12–18 years 200 mg twice daily

High-dose ritonavir (in combination with other antiretroviral drugs) for treatment of HIV infection, but tolerability is poor

• By mouth

Child 2–18 years initially 250 mg/m² twice daily, increased by 50 mg/m² at intervals of 2–3 days to 350 mg/m² twice daily (max. 600 mg twice daily)

Norvir® (AbbVie) (PoM)

Tablets, f/c, ritonavir 100 mg, net price 30-tab pack = £19.44. Label: 21, 25

Oral solution, sugar-free, ritonavir 400 mg/5 mL, net price 5 × 90-mL packs (with measuring cup) = £403.20. Label: 21, counselling, administration

Excipients include propylene glycol 26% (see Excipients, p. 2), alcohol 43%

Counselling Bitter taste of oral solution can be masked by mixing with chocolate milk; do not mix with water, measuring cup must be dry

With lopinavir

See under Lopinavir with ritonavir

TIPRANAVIR

Cautions see notes above; also patients at risk of increased bleeding from trauma, surgery, or other pathological conditions; concomitant use of drugs that increase risk of bleeding; **interactions:** Appendix 1 (tipranavir)

Hepatotoxicity Potentially life-threatening hepatotoxicity reported; monitor liver function before treatment then every 2 weeks for 1 month, then every 3 months. Discontinue if signs or symptoms of hepatitis develop or if liver-function abnormality develops (consult product literature)

Contra-indications see notes above

Hepatic impairment see notes above; also manufacturer advises caution in mild impairment; avoid in moderate or severe impairment—no information available

Pregnancy manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies

Breast-feeding see p. 314

Side-effects see notes above; also dyspnoea, anorexia, peripheral neuropathy, influenza-like symptoms, renal impairment, and photosensitivity; *rarely* dehydration

Indications and dose

HIV infection resistant to other protease inhibitors, in combination with other antiretroviral drugs in children previously treated with antiretrovirals

For dose, see preparations

Aptivus® (Boehringer Ingelheim) (PoM)

Capsules, pink, tipranavir 250 mg, net price 120-cap pack = £441.00. Label: 5, 21

Excipients include ethanol 100 mg per capsule

Dose

With low-dose ritonavir

- By mouth

Child 12–18 years 500 mg twice daily

Oral solution, toffee- and mint-flavoured, tipranavir 100 mg/mL, net price 95-mL pack = £129.65. Label: 5, 21, counselling, crystallisation

Excipients include vitamin E 78 mg/mL

Dose

With low-dose ritonavir

- By mouth

Child 2–12 years 375 mg/m² (max. 500 mg) twice daily

Note The bioavailability of Aptivus® oral solution is higher than that of the capsules; the oral solution is **not** interchangeable with the capsules on a milligram-for-milligram basis

Counselling Children and carers should be told to observe the oral solution for crystallisation; the bottle should be replaced if more than a thin layer of crystals form (doses should continue to be taken at the normal time until the bottle is replaced)

Non-nucleoside reverse transcriptase inhibitors

EFAVIRENZ

Cautions history of mental illness or seizures; monitor liver function if receiving other hepatotoxic drugs; **interactions:** Appendix 1 (efavirenz)

Rash Rash, usually in the first 2 weeks, is the most common side-effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption—usually resolves within 1 month

Psychiatric disorders Children or their carers should be advised to seek immediate medical attention if symptoms

such as severe depression, psychosis or suicidal ideation occur

Contra-indications acute porphyria (but see section 9.8.2)

Hepatic impairment in mild to moderate liver disease, monitor for dose-related side-effects (e.g. CNS effects) and liver function; avoid in severe impairment; greater risk of hepatic side-effects in chronic hepatitis B or C

Renal impairment manufacturer advises caution in severe renal failure—no information available

Pregnancy see p. 313; reports of neural tube defects when used in first trimester

Breast-feeding see p. 314

Side-effects rash including Stevens-Johnson syndrome (see Rash above); abdominal pain, diarrhoea, nausea, vomiting; anxiety, depression, sleep disturbances, abnormal dreams, dizziness, headache, fatigue, impaired concentration (administration at bedtime especially in first 2–4 weeks reduces CNS effects); pruritus; *less commonly* pancreatitis, hepatitis, flushing, psychosis, mania, suicidal ideation, amnesia, ataxia, tremor, convulsions, gynaecomastia, blurred vision, tinnitus; *rarely* hepatic failure, photosensitivity; also reported raised serum cholesterol (see Lipodystrophy syndrome, p. 314); see also Osteonecrosis, p. 315

Indications and dose

See Preparations

Sustiva® (Bristol-Myers Squibb) (PoM)

Capsules, efavirenz 50 mg (yellow/white), net price 30-cap pack = £16.73; 100 mg (white), 30-cap pack = £33.41; 200 mg (yellow), 90-cap pack = £200.27. Label: 23

Dose

HIV infection in combination with other antiretroviral drugs

- By mouth

Child 3–18 years

Body-weight 13–15 kg 200 mg once daily

Body-weight 15–20 kg 250 mg once daily

Body-weight 20–25 kg 300 mg once daily

Body-weight 25–32.5 kg 350 mg once daily

Body-weight 32.5–40 kg 400 mg once daily

Body-weight 40 kg and over 600 mg once daily

Administration Capsules may be opened and contents added to food (contents have a peppery taste) [unlicensed use]

Tablets, f/c, yellow, efavirenz 600 mg, net price 30-tab pack = £200.27. Label: 23

Dose

HIV infection in combination with other antiretroviral drugs

- By mouth

Child body-weight over 40 kg 600 mg once daily

Oral solution, sugar-free, strawberry and mint flavour, efavirenz 30 mg/mL, net price 180-mL pack = £53.84

Dose

HIV infection in combination with other antiretroviral drugs

- By mouth

Child 3–5 years

Body-weight 13–15 kg 360 mg once daily

Body-weight 15–20 kg 390 mg once daily

Body-weight 20–25 kg 450 mg once daily

Body-weight 25–32.5 kg 510 mg once daily

Child 5–18 years**Body-weight 13–15 kg** 270 mg once daily**Body-weight 15–20 kg** 300 mg once daily**Body-weight 20–25 kg** 360 mg once daily**Body-weight 25–32.5 kg** 450 mg once daily**Body-weight 32.5–40 kg** 510 mg once daily**Body-weight 40 kg and over** 720 mg once daily

Note The bioavailability of *Sustiva*® oral solution is lower than that of the capsules and tablets; the oral solution is **not** interchangeable with either capsules or tablets on a milligram-for-milligram basis

■ **With emtricitabine and tenofovir**

See under Tenofovir

ETRAVIRINE

Cautions interactions: Appendix 1 (etravirine)

Hypersensitivity reactions Rash, usually in the second week, is the most common side-effect and appears more frequently in females. Life-threatening hypersensitivity reactions reported usually during week 3–6 of treatment and characterised by rash, eosinophilia, and systemic symptoms (including fever, general malaise, myalgia, arthralgia, blistering, oral lesions, conjunctivitis, and hepatitis). Discontinue permanently if hypersensitivity reaction or severe rash develop. If rash mild or moderate (without signs of hypersensitivity reaction), may continue without interruption—usually resolves within 2 weeks

Counselling Children and carers should be told how to recognise hypersensitivity reactions and advised to seek immediate medical attention if hypersensitivity reaction or severe rash develop

Contra-indications acute porphyria (but see section 9.8.2)

Hepatic impairment use with caution in moderate impairment; avoid in severe impairment—no information available; greater risk of hepatic side-effects in chronic hepatitis B or C

Pregnancy see p. 313

Breast-feeding see p. 314

Side-effects rash (including Stevens-Johnson syndrome rarely and toxic epidermal necrolysis very rarely; see also Hypersensitivity Reactions above); gastro-oesophageal reflux, nausea, abdominal pain, flatulence, gastritis; hypertension; peripheral neuropathy; diabetes, hyperlipidaemia (see also Lipodystrophy Syndrome, p. 314); renal failure; anaemia; *less commonly* pancreatitis, haematemesis, hepatitis, chest pain, bronchospasm, drowsiness, malaise, gynaecomastia, blurred vision, dry mouth, and sweating; also reported, haemorrhagic stroke; see also Osteonecrosis, p. 315

Indications and dose

In combination with other antiretroviral drugs (including a boosted protease inhibitor) for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors

• By mouth

• **Child 6–18 years**

Body-weight 16–20 kg 100 mg twice daily**Body-weight 20–25 kg** 125 mg twice daily**Body-weight 25–30 kg** 150 mg twice daily**Body-weight over 30 kg** 200 mg twice daily

Missed dose If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time

Administration for children with swallowing difficulties, tablets may be dispersed in a glass of water just before administration

Intence® (Janssen) ▼ [PoM]

Tablets, etravirine 25 mg, net price 120-tab pack = £75.32; 100 mg, 120-tab pack = £301.27; 200 mg, 60-tab pack = £301.27. Label: 21, counselling, rash, and hypersensitivity reactions

Note Dispense in original container (contains desiccant)

NEVIRAPINE

Cautions chronic hepatitis B or C, high CD4 cell count, and females (all at greater risk of hepatic side-effects); **interactions**: Appendix 1 (nevirapine)

Hepatic disease Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in first 6 weeks; close monitoring required during first 18 weeks; monitor liver function before treatment then every 2 weeks for 2 months then after 1 month and then regularly; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction—discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction

Rash Rash, usually in first 6 weeks, is most common side-effect; incidence reduced if introduced at low dose and dose increased gradually; monitor closely for skin reactions during first 18 weeks; discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, facial oedema, general malaise or hypersensitivity reactions; if rash mild or moderate may continue without interruption but dose should not be increased until rash resolves

Counselling Children and carers should be told how to recognise hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if severe skin reaction, hypersensitivity reactions or symptoms of hepatitis develop

Contra-indications acute porphyria (but see section 9.8.2); post-exposure prophylaxis

Hepatic impairment manufacturer advises avoid modified-release preparation—no information available; use 'immediate-release' preparation with caution in moderate impairment and avoid in severe impairment; see also Hepatic Disease, above

Renal impairment manufacturer advises avoid modified-release preparation—no information available

Pregnancy see p. 313

Breast-feeding see p. 314

Side-effects rash including Stevens-Johnson syndrome and toxic epidermal necrolysis (see also Cautions above), nausea, vomiting, abdominal pain, diarrhoea, hepatitis (see also Hepatic Disease above), hypersensitivity reactions (may involve hepatic reactions and rash, see also Hepatic Disease above), headache, fatigue, fever, granulocytopenia; *less commonly* anaemia, myalgia, arthralgia; see also Osteonecrosis, p. 315

Licensed use 'immediate-release' tablets not licensed for use in children weighing less than 50 kg or with body surface area less than 1.25 m²; 'immediate-release' tablets and suspension not licensed for once daily dose after the initial dose titration

Indications and dose

HIV infection in combination with other anti-retroviral drugs

• By mouth

Child 1-month–3 years 150–200 mg/m² (max. 200 mg) once daily of 'immediate-release' preparation for first 14 days, then (if no rash present)

150–200 mg/m² (max. 200 mg) twice daily or 300–400 mg/m² (max. 400 mg) once daily of 'immediate-release' preparation

Child 3–18 years 150–200 mg/m² (max. 200 mg) once daily of 'immediate-release' preparation for first 14 days,

then (if no rash present after initial dose titration)

150–200 mg/m² (max. 200 mg) twice daily of 'immediate-release' preparation

or (if no rash present after initial dose titration)

Body surface area 0.58–0.83 m² 200 mg once daily of modified-release preparation or 'immediate-release' preparation

Body surface area 0.84–1.17 m² 300 mg once daily of modified-release preparation or 'immediate-release' preparation

Body surface area over 1.17 m² 400 mg once daily of modified-release preparation or 'immediate-release' preparation

Note Initial dose titration using 'immediate-release' preparation should not exceed 28 days; if rash not resolved within 28 days, alternative treatment should be sought. If treatment interrupted for more than 7 days, restart using the lower dose of the 'immediate-release' preparation for the first 14 days as for new treatment

Nevirapine (Non-proprietary) (PoM)

Tablets, nevirapine 200 mg, net price 60 = £170.00. Counselling, hypersensitivity reactions

Viramune® (Boehringer Ingelheim) (PoM)

Tablets, nevirapine 200 mg, net price 14-tab pack = £39.67, 60-tab pack = £170.00. Counselling, hypersensitivity reactions

Suspension, nevirapine 50 mg/5 mL, net price 240-mL pack = £50.40. Counselling, hypersensitivity reactions

Prolonged-release tablets, m/r, yellow, nevirapine 50 mg, net price 180-tab pack = £127.50; 100 mg, 90-tab pack = £127.50; 400 mg, 30-tab pack = £170.00. Label: 25, counselling, hypersensitivity reactions

Other antiretrovirals

DOLUTEGRAVIR

Cautions avoid concomitant use with etravirine, unless used in combination with atazanavir, darunavir, or lopinavir; **interactions**: Appendix 1 (dolutegravir)

Hypersensitivity reactions Hypersensitivity reactions (including severe rash, or rash accompanied by fever, malaise, arthralgia, myalgia, blistering, oral lesions, conjunctivitis, angioedema, eosinophilia, or raised liver enzymes) reported uncommonly. Discontinue immediately if any sign or symptoms of hypersensitivity reactions develop

Hepatic impairment manufacturer advises caution in severe impairment—no information available

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 314

Side-effects diarrhoea, nausea, vomiting, abdominal pain, flatulence, headache, dizziness, insomnia, abnormal dreams, fatigue, rash, pruritus, raised creatine kinase; *less commonly* hepatitis, hypersensitivity reactions (see Cautions); see also Osteonecrosis, p. 315

Indications and dose

In combination with other antiretroviral drugs for HIV infection without resistance to other inhibitors of HIV integrase

- By mouth

Child 12–18 years, body-weight over 40 kg consult product literature

Tivicay® (GSK) (PoM)

Tablets, yellow, f/c, dolutegravir (as sodium salt) 50 mg, net price 30-tab pack = £498.75. Counselling, antacids

Counselling Avoid antacids 6 hours before or 2 hours after taking dolutegravir

ENFUVIRTIDE

Cautions **interactions**: Appendix 1 (enfuvirtide)

Hypersensitivity reactions Hypersensitivity reactions including rash, fever, nausea, vomiting, chills, rigors, low blood pressure, respiratory distress, glomerulonephritis, and raised liver enzymes reported; discontinue immediately if any signs or symptoms of systemic hypersensitivity develop and do not rechallenge

Counselling Children and carers should be told how to recognise signs of hypersensitivity, and advised to discontinue treatment and seek prompt medical attention if symptoms develop

Hepatic impairment manufacturer advises caution—no information available; chronic hepatitis B or C (possibly greater risk of hepatic side-effects)

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 314

Side-effects injection-site reactions; pancreatitis, gastro-oesophageal reflux disease, anorexia, weight loss; hypertriglyceridaemia; peripheral neuropathy, asthenia, tremor, anxiety, nightmares, irritability, impaired concentration, vertigo; pneumonia, sinusitis, influenza-like illness; diabetes mellitus; haematuria; renal calculi, lymphadenopathy; myalgia; conjunctivitis; dry skin, acne, erythema, skin papilloma; *less commonly* hypersensitivity reactions (see Cautions); see also Osteonecrosis, p. 315

Indications and dose

HIV infection in combination with other antiretroviral drugs for resistant infection or for children intolerant to other antiretroviral regimens

- By subcutaneous injection

Child 6–16 years 2 mg/kg (max. 90 mg) twice daily

Child 16–18 years 90 mg twice daily

Administration for *subcutaneous injection*, reconstitute with 1.1 mL Water for Injections and allow to stand (for up to 45 minutes) to dissolve; do not shake or invert vial

Fuzeon® (Roche) (PoM)

Injection, powder for reconstitution, enfuvirtide 108 mg (= enfuvirtide 90 mg/mL when reconstituted with 1.1 mL Water for Injections), net price 108-mg vial = £18.03 (with solvent, syringe, and alcohol swabs). Counselling, hypersensitivity reactions

Electrolytes Na⁺ < 1 mmol/mL

MARAVIROC

Cautions cardiovascular disease; chronic hepatitis B or C; **interactions**: Appendix 1 (maraviroc)

Hepatic impairment use with caution

Renal impairment if estimated glomerular filtration rate less than 80 mL/minute/1.73 m², consult product literature

Pregnancy manufacturer advises use only if potential benefit outweighs risk—toxicity in *animal* studies

Breast-feeding see p. 314

Side-effects nausea, diarrhoea, abdominal pain, flatulence, anorexia, depression, insomnia, malaise, headache, anaemia, rash; *less commonly* seizures, renal failure, proteinuria, myositis; *rarely* hepatitis, angina, pancytopenia, granulocytopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis; also reported hypersensitivity reactions (including rash, fever, eosinophilia, and hepatic reactions); see also Osteonecrosis, p. 315

Licensed use not licensed for use in children

Indications and dose

CCR5-tropic HIV infection in combination with other antiretroviral drugs in children previously treated with antiretrovirals

For dose, consult Guidelines (see notes above)

Celsentri® (ViiV) (PoM)

Tablets, blue, f/c, maraviroc 150 mg, net price 60-tab pack = £441.27; 300 mg, 60-tab pack = £441.27

RALTEGRAVIR

Cautions risk factors for myopathy or rhabdomyolysis; psychiatric illness (may exacerbate underlying illness including depression); **interactions:** Appendix 1 (raltegravir)

Rash Rash occurs commonly. Discontinue if severe rash or rash accompanied by fever, malaise, arthralgia, myalgia, blistering, mouth ulceration, conjunctivitis, angioedema, hepatitis, or eosinophilia

Hepatic impairment chronic hepatitis B or C (greater risk of hepatic side-effects); use with caution in severe impairment—no information available

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding see p. 314

Side-effects diarrhoea, nausea, vomiting, dyspepsia, abdominal pain, flatulence, hypertriglyceridaemia, dizziness, headache, depression, insomnia, abnormal dreams, hyperactivity, asthenia, rash (including less commonly Stevens-Johnson syndrome, rash with eosinophilia and systemic symptoms; see also Rash above); *less commonly* gastritis, hepatitis, pancreatitis, dry mouth, taste disturbances, pain on swallowing, peptic ulcer, constipation, rectal bleeding, lipodystrophy (see Lipodystrophy Syndrome, p. 314), palpitation, ventricular extrasystoles, bradycardia, hypotension, flushing, chest pain, oedema, dysphonia, epistaxis, nasal congestion, drowsiness, anxiety, appetite changes, confusion, impaired memory and attention, suicidal ideation, pyrexia, chills, carpal tunnel syndrome, tremor, peripheral neuropathy, erectile dysfunction, gynaecomastia, menopausal symptoms, osteopenia, renal failure, nocturia, polydipsia, anaemia, thrombocytopenia, neutropenia, arthralgia, myalgia, rhabdomyolysis, visual disturbances, tinnitus, gingivitis, glossitis, acne, pruritus, hyperhidrosis, dry skin, skin papilloma, and alopecia; see also Osteonecrosis, p. 315

Indications and dose

See Preparations

Isentress® (MSD) (PoM)

Chewable tablets, orange- and banana-flavoured, raltegravir (as potassium salt) 25 mg (yellow), net price 60-tab pack = £32.74; 100 mg (orange), 60-tab pack

= £130.95. Label: 24

Excipients include aspartame (section 9.4.1)

Dose

In combination with other antiretroviral drugs for HIV infection resistant to multiple antiretrovirals

• By mouth

Child 2–12 years

Body-weight 12–14 kg 75 mg twice daily

Body-weight 14–20 kg 100 mg twice daily

Body-weight 20–28 kg 150 mg twice daily

Body-weight 28–40 kg 200 mg twice daily

Body-weight over 40 kg 300 mg twice daily

Important The bioavailability of *Isentress®* chewable tablets is higher than that of the 'standard' 400 mg tablets; the chewable tablets are **not** interchangeable with the 'standard' tablets on a milligram-for-milligram basis

Note Dispense in original container (contains desiccant)

Tablets ('standard'), pink, f/c, raltegravir (as potassium salt) 400 mg, net price 60-tab pack = £523.79. Label: 25

Dose

In combination with other antiretroviral drugs for HIV infection resistant to multiple antiretrovirals

• By mouth

Child 6–18 years and body-weight over 25 kg 400 mg twice daily

5.3.2 Herpesvirus infections

5.3.2.1 Herpes simplex and varicella-zoster infection

5.3.2.2 Cytomegalovirus infection

5.3.2.1 Herpes simplex and varicella-zoster infection

The two most important herpesvirus pathogens are herpes simplex virus (herpesvirus hominis) and varicella-zoster virus.

Herpes simplex infections Herpes infection of the mouth and lips and in the eye is generally associated with herpes simplex virus serotype 1 (HSV-1); other areas of the skin may also be infected, especially in immunodeficiency. Genital infection is most often associated with HSV-2 and also HSV-1. Treatment of herpes simplex infection should start as early as possible and usually within 5 days of the appearance of the infection. In individuals with good immune function, mild infection of the eye (ocular herpes, section 11.3.3) and of the lips (herpes labialis or cold sores, section 13.10.3) is treated with a topical antiviral drug. Primary herpetic gingivostomatitis is managed by changes to diet and with analgesics (section 12.3.2). Severe infection, neonatal herpes infection or infection in immunocompromised individuals requires treatment with a systemic antiviral drug. After completing parenteral treatment of neonatal herpes simplex encephalitis, oral suppression therapy with aciclovir for 6 months can be considered on specialist advice. Primary or recurrent genital herpes simplex infection is treated with an antiviral drug given by mouth. Persistence of a lesion or recurrence in an immunocompromised child may signal the development of resistance.

Specialist advice should be sought for systemic treatment of herpes simplex infection in pregnancy.

Varicella-zoster infections Regardless of immune function and the use of any immunoglobulins, neonates

with *chickenpox* should be treated with a parenteral antiviral to reduce the risk of severe disease. Oral therapy is not recommended as absorption is variable.

Chickenpox in otherwise healthy children between 1 month and 12 years is usually mild and antiviral treatment is not usually required. Chickenpox is more severe in adolescents than in children; antiviral treatment started within 24 hours of the onset of rash may reduce the duration and severity of symptoms in otherwise healthy adolescents. Antiviral treatment is generally recommended in immunocompromised patients and those at special risk (e.g. because of severe cardiovascular or respiratory disease or chronic skin disorder); in such cases, an antiviral is given for 10 days with at least 7 days of parenteral treatment.

In pregnancy severe chickenpox may cause complications, especially varicella pneumonia. Specialist advice should be sought for the treatment of chickenpox during pregnancy.

Neonates and children who have been exposed to chickenpox and are at special risk of complications may require prophylaxis with varicella-zoster immunoglobulin (see under Disease-specific Immunoglobulins, section 14.5.2). Prophylactic intravenous aciclovir should be considered for neonates whose mothers develop chickenpox 4 days before to 2 days after delivery.

In *herpes zoster* (shingles) systemic antiviral treatment can reduce the severity and duration of pain, reduce complications, and reduce viral shedding. Treatment with the antiviral should be started within 72 hours of the onset of rash and is usually continued for 7–10 days. Immunocompromised patients at high risk of disseminated or severe infection should be treated with a parenteral antiviral drug. Chronic pain which persists after the rash has healed (postherpetic neuralgia) requires specific management (section 4.7.3).

Choice Aciclovir is active against herpesviruses but does not eradicate them. Uses of aciclovir include systemic treatment of varicella-zoster and the systemic and topical treatment of herpes simplex infections of the skin (section 13.10.3) and mucous membranes (section 7.2.2). It is used by mouth for severe herpetic stomatitis (see also p. 551). Aciclovir eye ointment (section 11.3.3) is used for herpes simplex infections of the eye; it is combined with systemic treatment for ophthalmic zoster.

Famciclovir, a prodrug of penciclovir, is similar to aciclovir and is licensed in adults for use in herpes zoster and genital herpes; there is limited information available on use in children. Penciclovir itself is used as a cream for herpes simplex labialis (section 13.10.3).

Valaciclovir is an ester of aciclovir, licensed in adults for herpes zoster and herpes simplex infections of the skin and mucous membranes (including genital herpes); it is also licensed in children over 12 years for preventing cytomegalovirus disease following solid organ transplantation. Valaciclovir may be used for the treatment of mild herpes zoster in immunocompromised children over 12 years; treatment should be initiated under specialist supervision.

ACICLOVIR (Acyclovir)

Cautions maintain adequate hydration (especially with infusion or high doses, or during renal impairment); **interactions:** Appendix 1 (aciclovir)

Renal impairment see Cautions above; also risk of neurological reactions increased; use normal *intra-*

venous dose every 12 hours if estimated glomerular filtration rate 25–50 mL/minute/1.73 m² (every 24 hours if estimated glomerular filtration rate 10–25 mL/minute/1.73 m²); consult product literature for intravenous dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m². For *herpes zoster*, use normal oral dose every 8 hours if estimated glomerular filtration rate 10–25 mL/minute/1.73 m² (every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²). For *herpes simplex*, use normal oral dose every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy not known to be harmful—manufacturers advise use only when potential benefit outweighs risk

Breast-feeding significant amount in milk after systemic administration; not known to be harmful but manufacturers advise caution

Side-effects nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, photosensitivity; *very rarely* hepatitis, jaundice, dyspnoea, neurological reactions (including dizziness, confusion, hallucinations, convulsions, ataxia, dysarthria, and drowsiness), acute renal failure, anaemia, thrombocytopenia, and leucopenia; *on intravenous infusion*, severe local inflammation (sometimes leading to ulceration), and *very rarely* agitation, tremors, psychosis and fever

Licensed use tablets and suspension not licensed for suppression of herpes simplex or for treatment of herpes zoster in children (age range not specified by manufacturer); intravenous infusion not licensed for herpes zoster in children under 18 years; tablets and suspension not licensed for attenuation of chickenpox (if varicella-zoster immunoglobulin not indicated) in children under 18 years

Indications and dose

Herpes simplex treatment

• By mouth

Child 1 month–2 years 100 mg 5 times daily, usually for 5 days (longer if new lesions appear during treatment or if healing incomplete); dose doubled if immunocompromised or if absorption impaired

Child 2–18 years 200 mg 5 times daily, usually for 5 days (longer if new lesions appear during treatment or if healing incomplete); dose doubled if immunocompromised or if absorption impaired

• By intravenous infusion

Neonate 20 mg/kg every 8 hours for 14 days (for at least 21 days if CNS involvement—confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment)

Child 1–3 months 20 mg/kg every 8 hours for 14 days (for at least 21 days if CNS involvement—confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment)

Child 3 months–12 years 250 mg/m² every 8 hours usually for 5 days, doubled to 500 mg/m² every 8 hours in the immunocompromised or in simplex encephalitis (given for at least 21 days in encephalitis—confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment)

Child 12–18 years 5 mg/kg every 8 hours usually for 5 days, doubled to 10 mg/kg every 8 hours in

the immunocompromised or in simplex encephalitis (given for at least 14 days in encephalitis (at least 21 days if also immunocompromised)—confirm cerebrospinal fluid negative for herpes simplex virus before stopping treatment)

Note To avoid excessive dose in obese patients parenteral dose should be calculated on the basis of ideal weight for height

Herpes simplex prophylaxis in the immunocompromised

• By mouth

Child 1 month–2 years 100–200 mg 4 times daily

Child 2–18 years 200–400 mg 4 times daily

Herpes simplex suppression

• By mouth

Child 12–18 years 400 mg twice daily or 200 mg 4 times daily; increased to 400 mg 3 times daily if recurrences occur on standard suppressive therapy or for suppression of genital herpes during late pregnancy (from 36 weeks gestation); therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

Chickenpox and herpes zoster infection

• By mouth

Child 1 month–2 years 200 mg 4 times daily for 5 days (for herpes zoster in the immunocompromised continue for 2 days after crusting of lesions)

Child 2–6 years 400 mg 4 times daily for 5 days (for herpes zoster in the immunocompromised continue for 2 days after crusting of lesions)

Child 6–12 years 800 mg 4 times daily for 5 days (for herpes zoster in the immunocompromised continue for 2 days after crusting of lesions)

Child 12–18 years 800 mg 5 times daily for 7 days (for herpes zoster in the immunocompromised continue for 2 days after crusting of lesions)

• By intravenous infusion

Neonate 10–20 mg/kg every 8 hours for at least 7 days (given for 10–14 days in encephalitis, possibly longer if also immunocompromised)

Child 1–3 months 10–20 mg/kg every 8 hours for at least 7 days (given for 10–14 days in encephalitis, possibly longer if also immunocompromised)

Child 3 months–12 years 250 mg/m² every 8 hours usually for 5 days, doubled to 500 mg/m² every 8 hours in the immunocompromised or in encephalitis (given for 10–14 days in encephalitis, possibly longer if also immunocompromised)

Child 12–18 years 5 mg/kg every 8 hours usually for 5 days, doubled to 10 mg/kg every 8 hours in the immunocompromised or in encephalitis (given for 10–14 days in encephalitis, possibly longer if also immunocompromised)

Note To avoid excessive dose in obese patients parenteral dose should be calculated on the basis of ideal weight for height

Prophylaxis of chickenpox after delivery (see notes above)

• By intravenous infusion

Neonate 10 mg/kg every 8 hours; continued until serological tests confirm absence of virus

Attenuation of chickenpox if varicella–zoster immunoglobulin not indicated

• By mouth

Child 1 month–18 years 10 mg/kg 4 times daily for 7 days starting 1 week after exposure

Herpesvirus skin infections section 13.10.3

Herpesvirus eye infections section 11.3.3

Administration for *intravenous infusion*, reconstitute to 25 mg/mL with Water for Injections or Sodium Chloride 0.9% then dilute to concentration of 5 mg/mL with Sodium Chloride 0.9% or Sodium Chloride and Glucose and give over 1 hour; alternatively, may be administered in a concentration of 25 mg/mL using a suitable infusion pump and central venous access and given over 1 hour

Aciclovir (Non-proprietary) (PoM)

Tablets, aciclovir 200 mg, net price 25-tab pack = £1.66; 400 mg, 56-tab pack = £4.30; 800 mg, 35-tab pack = £4.30. Label: 9

Dental prescribing on NHS Aciclovir Tablets 200 mg or 800 mg may be prescribed

Dispersible tablets, aciclovir 200 mg, net price 25-tab pack = £2.17; 400 mg, 56-tab pack = £9.68; 800 mg, 35-tab pack = £9.10. Label: 9

Suspension, aciclovir 200 mg/5 mL, net price 125 mL = £35.59; 400 mg/5 mL, 100 mL = £39.27. Label: 9

Dental prescribing on NHS Aciclovir Oral Suspension 200 mg/5 mL may be prescribed

Intravenous infusion, powder for reconstitution, aciclovir (as sodium salt), net price 250-mg vial = £9.13; 500-mg vial = £20.22

Electrolytes Na⁺ 1.1 mmol/250-mg vial

Intravenous infusion, aciclovir (as sodium salt), 25 mg/mL, net price 10-mL (250-mg) vial = £10.18; 20-mL (500-mg) vial = £19.61; 40-mL (1-g) vial = £40.44

Electrolytes Na⁺ 1.16 mmol/250-mg vial

Zovirax® (GSK) (PoM)

Tablets, all dispersible, f/c, aciclovir 200 mg, net price 25-tab pack = £2.85; 800 mg (scored, *Shingles Treatment Pack*), 35-tab pack = £10.50. Label: 9

Suspension, both off-white, sugar-free, aciclovir 200 mg/5 mL (banana-flavoured), net price 125 mL = £29.56; 400 mg/5 mL (*Double Strength Suspension*, orange-flavoured), 100 mL = £33.02. Label: 9

Intravenous infusion, powder for reconstitution, aciclovir (as sodium salt), net price 250-mg vial = £3.34; 500-mg vial = £3.40

Electrolytes Na⁺ 1.1 mmol/250-mg vial

VALACICLOVIR

Note Valaciclovir is a pro-drug of aciclovir

Cautions see under Aciclovir

Hepatic impairment manufacturer advises caution with high doses used for preventing cytomegalovirus disease—no information available in children

Renal impairment maintain adequate hydration; for *herpes zoster*, 1 g every 12 hours if estimated glom-

erular filtration rate 30–50 mL/minute/1.73 m² (1 g every 24 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; 500 mg every 24 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²); for *treatment of herpes simplex*, 500 mg (1 g in immunocompromised or HIV-positive children) every 24 hours if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; for *treatment of herpes labialis*, if estimated glomerular filtration rate 30–50 mL/minute/1.73 m², initially 1 g, then 1 g 12 hours after initial dose (if estimated glomerular filtration rate 10–30 mL/minute/1.73 m², initially 500 mg, then 500 mg 12 hours after initial dose; if estimated glomerular filtration rate less than 10 mL/minute/1.73 m², 500 mg as a single dose); for *suppression of herpes simplex*, 250 mg (500 mg in immunocompromised or HIV-positive children) every 24 hours if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; reduce dose according to estimated glomerular filtration rate for *cytomegalovirus prophylaxis* following solid organ transplantation (consult product literature)

Pregnancy see under Aciclovir

Breast-feeding see under Aciclovir

Side-effects see under Aciclovir but neurological reactions more frequent with high doses

Licensed use not licensed for treatment of herpes zoster in children; not licensed for treatment or suppression of herpes simplex infection in immunocompromised or HIV-positive children

Indications and dose

Herpes zoster in immunocompromised

- By mouth

Child 12–18 years 1 g 3 times daily for at least 7 days (continue for 2 days after crusting of lesions)

Treatment of herpes simplex

- By mouth

Child 12–18 years first episode, 500 mg twice daily for 5 days, longer if new lesions appear during treatment or if healing incomplete (1 g twice daily for 10 days in immunocompromised or HIV-positive children); recurrent infection, 500 mg twice daily for 3–5 days (1 g twice daily for 5–10 days in immunocompromised or HIV-positive children)

Treatment of herpes labialis

- By mouth

Child 12–18 years initially 2 g, then 2 g 12 hours after initial dose

Suppression of herpes simplex

- By mouth

Child 12–18 years 500 mg daily in 1–2 divided doses (in immunocompromised or HIV-positive children, 500 mg twice daily); therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

Prevention of cytomegalovirus disease following solid organ transplantation (preferably starting within 72 hours of transplantation)

- By mouth

Child 12–18 years 2 g 4 times daily usually for 90 days

Valaciclovir (Non-proprietary) (PoM)

Tablets, valaciclovir 500 mg, net price 10-tab pack = £3.83, 42 tab-pack = £8.50. Label: 9

Valtrex® (GSK) (PoM)

Tablets, f/c, valaciclovir (as hydrochloride) 250 mg, net price 60-tab pack = £123.28; 500 mg, 10-tab pack = £20.59, 42-tab pack = £86.30. Label: 9

5.3.2.2 Cytomegalovirus infection

Ganciclovir is related to aciclovir but it is more active against cytomegalovirus (CMV); it is also much more toxic than aciclovir and should therefore be prescribed under specialist supervision and only when the potential benefit outweighs the risks. Ganciclovir is administered by intravenous infusion for the *initial treatment* of CMV infection. The use of ganciclovir may also be considered for symptomatic congenital CMV infection. Ganciclovir causes profound myelosuppression when given with zidovudine; the two should not normally be given together particularly during initial ganciclovir therapy. The likelihood of ganciclovir resistance increases in patients with a high viral load or in those who receive the drug over a long duration; cross-resistance to cidofovir is common.

Valaciclovir (section 5.3.2.1) is licensed for use in children over 12 years for prevention of cytomegalovirus disease following renal transplantation.

Foscarnet is also active against cytomegalovirus; it is toxic and can cause renal impairment. It is deposited in teeth, bone and cartilage, and *animal* studies have shown that deposition is greater in young animals. Its effect on skeletal development in children is not known. Foscarnet should be prescribed under specialist supervision.

Cidofovir is given in combination with probenecid for CMV retinitis in AIDS patients when ganciclovir and foscarnet are contra-indicated. Cidofovir is nephrotoxic. There is limited information on its use in children.

GANCICLOVIR

Cautions close monitoring of full blood count (severe deterioration may require correction and possibly treatment interruption); history of cytopenia; potential carcinogen and teratogen; radiotherapy; ensure adequate hydration during intravenous administration; vesicant—infuse into vein with adequate flow preferably using plastic cannula; possible risk of long-term carcinogenic or reproductive toxicity; **interactions**: Appendix 1 (ganciclovir)

Contra-indications hypersensitivity to valganciclovir, ganciclovir, aciclovir, or valaciclovir; abnormally low haemoglobin, neutrophil, or platelet counts (consult product literature)

Renal impairment reduce dose if estimated glomerular filtration rate less than 70 mL/minute/1.73 m²; consult product literature

Pregnancy avoid—teratogenic risk; ensure effective contraception during treatment and barrier contraception for males during and for at least 90 days after treatment

Breast-feeding avoid—no information available

Side-effects diarrhoea, nausea, vomiting, dyspepsia, abdominal pain, constipation, flatulence, dysphagia, taste disturbance, hepatic dysfunction; dyspnoea,

chest pain, cough; headache, insomnia, convulsions, dizziness, peripheral neuropathy, depression, anxiety, confusion, abnormal thinking, fatigue, weight loss, anorexia; infection, pyrexia, night sweats; anaemia, leucopenia, thrombocytopenia, pancytopenia, renal impairment; myalgia, arthralgia; macular oedema, retinal detachment, vitreous floaters, eye pain; ear pain; dermatitis, pruritus; injection-site reactions; *less commonly* mouth ulcers, pancreatitis, arrhythmias, hypotension, anaphylactic reactions, psychosis, tremor, male infertility, haematuria, disturbances in hearing and vision, and alopecia

Licensed use not licensed for use in children

Indications and dose

Life-threatening or sight-threatening cytomegalovirus infections in immunocompromised patients only; prevention of cytomegalovirus disease during immunosuppressive therapy following organ transplantation

• By intravenous infusion

Child 1 month–18 years initially (induction) 5 mg/kg every 12 hours for 14–21 days for treatment or for 7–14 days for prevention; maintenance (for patients at risk of relapse of retinitis), 6 mg/kg daily on 5 days per week or 5 mg/kg daily until adequate recovery of immunity; if retinitis progresses initial induction treatment may be repeated

Congenital cytomegalovirus infection of the CNS

• By intravenous infusion

Neonate 6 mg/kg every 12 hours for 6 weeks

Local treatment of CMV retinitis section 11.3.3

Administration for *intravenous infusion*, reconstitute with Water for Injections (500 mg/10 mL) then dilute to a concentration of not more than 10 mg/mL with Glucose 5% or Sodium Chloride 0.9% and give over 1 hour

Cymevene® (Roche) (PoM)

Intravenous infusion, powder for reconstitution, ganciclovir (as sodium salt). Net price 500-mg vial = £29.77

Electrolytes Na⁺ 2 mmol/500-mg vial

Caution in handling Ganciclovir is toxic and personnel should be adequately protected during handling and administration; if solution comes into contact with skin or mucosa, wash off immediately with soap and water

FOSCARNET SODIUM

Cautions see Cytomegalovirus Infection above; monitor electrolytes, particularly calcium and magnesium; monitor serum creatinine every second day during induction and every week during maintenance; ensure adequate hydration; avoid rapid infusion; men should avoid fathering a child during and for 6 months after treatment; **interactions:** Appendix 1 (foscarnet)

Renal impairment reduce dose; consult product literature

Pregnancy avoid

Breast-feeding avoid—present in milk in *animal* studies

Side-effects nausea (reduce infusion rate), vomiting, diarrhoea, abdominal pain, constipation, dyspepsia, anorexia, hepatic dysfunction, pancreatitis, changes in blood pressure and ECG, palpitation, oedema,

dizziness, headache, malaise, aggression, agitation, anxiety, confusion, depression, paraesthesia (reduce infusion rate), convulsions, tremor, and other neurological disorders, anaemia, granulocytopenia, leucopenia, thrombocytopenia, dysuria, polyuria, renal impairment including acute renal failure, electrolyte disturbances (including hypokalaemia, hypomagnesaemia, and hypocalcaemia), myalgia, rash, pruritus, thrombophlebitis if given undiluted by peripheral vein, genital irritation and ulceration (due to high concentrations excreted in urine); *less commonly* acidosis; also reported oesophageal ulceration, ventricular arrhythmias, diabetes insipidus, myasthenia, myositis, rhabdomyolysis

Licensed use not licensed for use in children

Indications and dose

CMV disease

• By intravenous infusion

Child 1 month–18 years induction 60 mg/kg every 8 hours for 2–3 weeks then maintenance 60 mg/kg daily, increased to 90–120 mg/kg if tolerated; if disease progresses on maintenance dose, repeat induction regimen

Mucocutaneous herpes simplex infection

• By intravenous infusion

Child 1 month–18 years 40 mg/kg every 8 hours for 2–3 weeks or until lesions heal

Administration for *intravenous infusion*, give undiluted solution via a central venous catheter; alternatively dilute to a concentration of 12 mg/mL with Glucose 5% or Sodium Chloride 0.9% for administration via a peripheral vein; give over at least 1 hour (give doses greater than 60 mg/kg over 2 hours)

Foscavir® (Clingen) (PoM)

Intravenous infusion, foscarnet sodium hexahydrate 24 mg/mL, net price 250-mL bottle = £119.85

Electrolytes Na⁺ 0.24 mmol/mL

5.3.3 Viral hepatitis

Treatment for viral hepatitis should be initiated by a specialist in hepatology or infectious diseases. The management of uncomplicated acute viral hepatitis is largely symptomatic. Hepatitis B and hepatitis C viruses are major causes of chronic hepatitis. For details on immunisation against hepatitis A and B infections, see section 14.4 (active immunisation) and section 14.5 (passive immunisation).

Chronic hepatitis B Interferon alfa (section 8.2.4), peginterferon alfa-2a, lamivudine (section 5.3.1), **adefovir dipivoxil**, **entecavir**, and **tenofovir disoproxil** have a role in the treatment of chronic hepatitis B in adults, but their role in children has not been well established. Specialist supervision is required for the management of chronic hepatitis B.

Tenofovir, or a combination of tenofovir with either emtricitabine or lamivudine, may be used with other antiretrovirals, as part of 'highly active antiretroviral therapy' (section 5.3.1) in children who require treatment for both HIV and chronic hepatitis B. If children infected with both HIV and chronic hepatitis B only require treatment for chronic hepatitis B, they should receive antivirals that are not active against HIV. Management of these children should be co-ordinated between HIV and hepatology specialists.

Chronic hepatitis C Treatment should be considered for children with moderate or severe liver disease. Specialist supervision is required and the regimen is chosen according to the genotype of the infecting virus and the viral load. A combination of **ribavirin** (section 5.3.5) with either **interferon alfa** (section 8.2.4) or **peginterferon alfa-2b** is licensed for use in children over 3 years with chronic hepatitis C. A combination of peginterferon alfa (section 8.2.4) and ribavirin is preferred.

NICE guidance

Peginterferon alfa and ribavirin for chronic hepatitis C (November 2013)

Peginterferon alfa in combination with ribavirin is recommended (within the marketing authorisation) as an option for treating chronic hepatitis C in children.

www.nice.org.uk/TA300

5.3.4 Influenza

For advice on immunisation against influenza, see section 14.4.

Oseltamivir and **zanamivir** reduce replication of influenza A and B viruses by inhibiting viral neuraminidase. They are most effective for the treatment of influenza if started within a few hours of the onset of symptoms; oseltamivir is licensed for use within 48 hours of the first symptoms while zanamivir is licensed for use within 36 hours of the first symptoms. In otherwise healthy individuals they reduce the duration of symptoms by about 1–1.5 days. For further information on the treatment of influenza, see NICE guidance, below.

Oseltamivir and zanamivir are licensed for post-exposure prophylaxis of influenza when influenza is circulating in the community. Oseltamivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza (see also NICE guidance, below). However, in children with severe influenza or in those who are immunocompromised, antivirals may still be effective after this time if viral shedding continues [unlicensed use]. Oseltamivir and zanamivir are also licensed for use in exceptional circumstances (e.g. when vaccination does not cover the infecting strain) to prevent influenza in an epidemic.

There is evidence that some strains of influenza A virus have reduced susceptibility to oseltamivir, but may retain susceptibility to zanamivir. Resistance to oseltamivir may be greater in severely immunocompromised children.

Zanamivir should be reserved for patients who are severely immunocompromised, or when oseltamivir cannot be used, or when resistance to oseltamivir is suspected. For those unable to use the dry powder for inhalation, zanamivir is available as a solution that can be administered by nebuliser or intravenously [unlicensed].

Oseltamivir in children under 1 year of age

Data on the use of oseltamivir in children under 1 year of age is limited. Furthermore, oseltamivir may be ineffective in neonates because they may not be able to metabolise oseltamivir to its active form. However, oseltamivir can be used (under specialist supervision) for the treatment or post-exposure prophylaxis of influenza in children under 1 year of age. The Department of Health has advised (May 2009) that during a pandemic,

treatment with oseltamivir can be overseen by health-care professionals experienced in assessing children.

Amantadine is licensed for prophylaxis and treatment of influenza A in children over 10 years of age, but it is no longer recommended (see NICE guidance, below).

Information on pandemic influenza, avian influenza, and swine influenza can be found at www.hpa.org.uk.

Pregnancy and breast-feeding

Although safety data are limited, either oseltamivir or zanamivir can be used in women who are pregnant or breast-feeding when the potential benefit outweighs the risk (e.g. during a pandemic). Oseltamivir is the preferred drug in women who are breast-feeding.

NICE guidance

Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008)

The drugs described here are not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

- Amantadine is **not** recommended for prophylaxis of influenza.
- Oseltamivir or zanamivir are **not** recommended for seasonal prophylaxis against influenza.
- When influenza is circulating in the community¹, either oseltamivir or zanamivir is recommended (in accordance with UK licensing) for post-exposure prophylaxis in at-risk patients who are not effectively protected by influenza vaccine, and who have been in close contact with someone suffering from influenza-like illness in the same household or residential setting. Oseltamivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza.
- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, either oseltamivir or zanamivir may be used for post-exposure prophylaxis in at-risk patients (regardless of influenza vaccination) living in long-term residential or nursing homes.

At-risk² patients are those who have one or more of the following conditions:

- chronic respiratory disease (including asthma);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/TA158

1. National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.
2. The Department of Health in England has advised (November 2010 and April 2011) that 'at risk patients' also includes children who are at risk of developing medical complications from influenza (treatment only) or females who are pregnant.

NICE guidance**Oseltamivir, zanamivir, and amantadine for treatment of influenza (February 2009)**

The drugs described here are not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

- Amantadine is **not** recommended for treatment of influenza.
- When influenza is circulating in the community¹, either oseltamivir or zanamivir is recommended (in accordance with UK licensing) for the treatment of influenza in at-risk patients who can start treatment within 48 hours (within 36 hours for zanamivir) of the onset of symptoms.
- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, either oseltamivir or zanamivir may be used for treatment in at-risk patients living in long-term residential or nursing homes.

At-risk² patients are those who have one or more of the following conditions:

- chronic respiratory disease (including asthma);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

www.nice.org.uk/TA168

OSELTAMIVIR

Renal impairment for *treatment*, use 40% of normal dose twice daily if estimated glomerular filtration rate 30–60 mL/minute/1.73 m² (40% of normal dose once daily if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²); for *prevention*, use 40% of normal dose once daily if estimated glomerular filtration rate 30–60 mL/minute/1.73 m² (40% of normal dose every 48 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²); avoid for *treatment* and *prevention* if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy use only if potential benefit outweighs risk (e.g. during a pandemic); see also p. 330

Breast-feeding amount probably too small to be harmful; use only if potential benefit outweighs risk; (e.g. during a pandemic); see also p. 330

Side-effects nausea, vomiting, abdominal pain, dyspepsia, headache; *less commonly* arrhythmias, convulsions, altered consciousness, eczema, rash; *rarely* hepatitis, gastro-intestinal bleeding, neuropsychiatric disorders, thrombocytopenia, visual disturbances, Stevens-Johnson syndrome, toxic epidermal necrolysis

Licensed use not licensed for use in children under 1 year unless there is a pandemic

1. National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.
2. The Department of Health in England has advised (November 2010 and April 2011) that 'at risk patients' also includes children who are at risk of developing medical complications from influenza (treatment only) or females who are pregnant.

Indications and dose**Prevention of influenza**

• By mouth

Neonate (see notes above) 2 mg/kg once daily for 10 days for post-exposure prophylaxis

Child 1–3 months (see notes above) 2.5 mg/kg once daily for 10 days for post-exposure prophylaxis

Child 3 months–1 year (see notes above) 3 mg/kg once daily for 10 days for post-exposure prophylaxis

Child 1–13 years

Body-weight 10–15 kg 30 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic

Body-weight 15–23 kg 45 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic

Body-weight 23–40 kg 60 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic

Body-weight over 40 kg 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic

Child 13–18 years 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic

Treatment of influenza

• By mouth

Neonate (see notes above) 2 mg/kg twice daily for 5 days

Child 1–3 months (see notes above) 2.5 mg/kg twice daily for 5 days

Child 3 months–1 year (see notes above) 3 mg/kg twice daily for 5 days

Child 1–13 years

Body-weight 10–15 kg 30 mg twice daily for 5 days

Body-weight 15–23 kg 45 mg twice daily for 5 days

Body-weight 23–40 kg 60 mg twice daily for 5 days

Body-weight over 40 kg 75 mg twice daily for 5 days

Child 13–18 years 75 mg twice daily for 5 days

Administration if suspension not available, capsules can be opened and the contents mixed with a small amount of sweetened food, such as sugar water or chocolate syrup, just before administration

3 Tamiflu® (Roche) (PoM)

Capsules, oseltamivir (as phosphate) 30 mg (yellow), net price 10-cap pack = £7.71; 45 mg (grey), 10-cap pack = £15.41; 75 mg (grey-yellow), 10-cap pack = £15.41. Label: 9

Oral suspension, sugar-free, tutti-frutti-flavoured, oseltamivir (as phosphate) for reconstitution with water, 30 mg/5 mL, net price 65 mL = £10.27. Label: 9

Excipients include sorbitol 900 mg/5 mL

Note Solutions prepared by 'Special Order' manufacturers may be a different concentration

3. **Use** except for the treatment and prophylaxis of influenza as indicated in the notes above and NICE guidance; endorse prescription 'SL5'

ZANAMIVIR

Cautions asthma and chronic pulmonary disease (risk of bronchospasm—short-acting bronchodilator should be available; avoid in severe asthma unless close monitoring possible and appropriate facilities available to treat bronchospasm); uncontrolled chronic illness; other inhaled drugs should be administered before zanamivir

Pregnancy use only if potential benefit outweighs risk (e.g. during a pandemic); see also p. 330

Breast-feeding amount probably too small to be harmful; use only if potential benefit outweighs risk (e.g. during a pandemic); see also p. 330

Side-effects rash; *less commonly* bronchospasm, dyspnoea, angioedema, urticaria; *rarely* Stevens-Johnson syndrome, toxic epidermal necrolysis; also reported neuropsychiatric disorders

Indications and dose

Post-exposure prophylaxis of influenza

- By inhalation of powder

Child 5–18 years 10 mg once daily for 10 days

Prevention of influenza during an epidemic

- By inhalation of powder

Child 5–18 years 10 mg once daily for up to 28 days

Treatment of influenza

- By inhalation of powder

Child 5–18 years 10 mg twice daily for 5 days (for up to 10 days if resistance to oseltamivir suspected)

¹ Relenza® (GSK) (PoM)

Dry powder for inhalation disks containing 4 blisters of zanamivir 5 mg/blister, net price 5 disks with Diskhaler® device = £16.36

5.3.5 Respiratory syncytial virus

Ribavirin inhibits a wide range of DNA and RNA viruses. It is licensed for administration by inhalation for the treatment of severe bronchiolitis caused by the respiratory syncytial virus (RSV) in infants, especially when they have other serious diseases. However, there is no evidence that ribavirin produces clinically relevant benefit in RSV bronchiolitis. Ribavirin is given by mouth with peginterferon alpha or interferon alpha for the treatment of chronic hepatitis C infection (see Viral Hepatitis, section 5.3.3). Ribavirin is also effective in Lassa fever and has also been used parenterally in the treatment of life-threatening RSV, parainfluenza virus, and adenovirus infections in immunocompromised children (unlicensed indications).

Palivizumab is a monoclonal antibody licensed for preventing serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease; it should be prescribed under specialist supervision and on the basis of the likelihood of hospitalisation.

Palivizumab is recommended for:

- children under 9 months of age with chronic lung disease (defined as requiring oxygen for at least 28 days from birth) and who were born preterm²;
- children under 6 months of age with haemodynamically significant, acyanotic congenital heart disease who were born preterm².

Palivizumab should be considered for:

- children under 2 years of age with severe combined immunodeficiency syndrome;
- children under 1 year of age who require long-term ventilation;
- children 1–2 years of age who require long-term ventilation and have an additional co-morbidity (including cardiac disease or pulmonary hypertension).

PALIVIZUMAB

Cautions moderate to severe acute infection or febrile illness; thrombocytopenia; serum-palivizumab concentration may be reduced after cardiac surgery; hypersensitivity to humanised monoclonal antibodies

Side-effects fever, injection-site reactions, nervousness; *less commonly* diarrhoea, vomiting, constipation, haemorrhage, rhinitis, cough, wheeze, pain, drowsiness, asthenia, hyperkinesia, leucopenia, and rash; also reported, apnoea, hypersensitivity reactions (including anaphylaxis), convulsions and thrombocytopenia

Licensed use licensed for the prevention of serious lower respiratory-tract disease caused by respiratory syncytial virus (RSV) in children under 6 months of age (at the start of the RSV season) and born at less than 35 weeks corrected gestational age, or in children under 2 years of age who have received treatment for bronchopulmonary dysplasia in the last 6 months, or in children under 2 years of age with haemodynamically significant congenital heart disease

Indications and dose

Prevention of serious disease caused by respiratory syncytial virus infection (see notes above)

- By intramuscular injection (preferably in antero-lateral thigh)

Neonate 15 mg/kg once a month during season of RSV risk

Child 1 month–2 years 15 mg/kg once a month during season of RSV risk (child undergoing cardiac bypass surgery, 15 mg/kg as soon as stable after surgery, then once a month during season of risk); injection volume over 1 mL should be divided between 2 or more sites

Synagis® (AbbVie) (PoM)

Injection, powder for reconstitution, palivizumab, net price 50-mg vial = £306.34; 100-mg vial = £563.64

1. ¹ except for the treatment and prophylaxis of influenza as indicated in the notes above and NICE guidance; endorse prescription 'SL5'

2. For details of the preterm age groups included in the recommendations, see *Immunisation against Infectious Disease* (2006), available at www.gov.uk/dh

RIBAVIRIN (Tribavirin)

Cautions

Specific cautions for inhaled treatment Maintain standard supportive respiratory and fluid management therapy; monitor electrolytes closely; monitor equipment for precipitation; pregnant women (and those planning pregnancy) should avoid exposure to aerosol

Specific cautions for systemic treatment Exclude pregnancy before treatment in females of childbearing age; effective contraception essential during treatment and for 4 months after treatment in females and for 7 months after treatment in males of childbearing age; routine monthly pregnancy tests recommended; condoms must be used if partner of male patient is pregnant (ribavirin excreted in semen); cardiac disease (assessment including ECG recommended before and during treatment—discontinue if deterioration); determine full blood count, platelets, electrolytes, serum creatinine, liver function tests and uric acid before starting treatment and then on weeks 2 and 4 of treatment, then as indicated clinically—adjust dose if adverse reactions or laboratory abnormalities develop (consult product literature); eye examination recommended before oral treatment; eye examination also recommended during oral treatment if pre-existing ophthalmological disorder or if decrease in vision reported—discontinue treatment if ophthalmological disorder deteriorates or if new ophthalmological disorder develops; test thyroid function before treatment and then every 3 months; patients with a transplant—risk of rejection; risk of growth retardation, the reversibility of which is uncertain—if possible, consider starting treatment after pubertal growth spurt

Interactions: Appendix 1 (ribavirin)

Contra-indications

Specific contra-indications for systemic treatment Severe, uncontrolled cardiac disease in children with chronic hepatitis C; haemoglobinopathies; severe debilitating medical conditions; autoimmune disease (including autoimmune hepatitis); history of severe psychiatric condition

Hepatic impairment no dosage adjustment required; use oral ribavirin with caution in severe hepatic dysfunction or decompensated cirrhosis

Renal impairment plasma-ribavirin concentration increased; manufacturer advises avoid oral ribavirin if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²; manufacturer advises use intravenous preparation with caution if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy avoid; teratogenicity in animal studies; see also Cautions above

Breast-feeding avoid—no information available

Side-effects

Specific side-effects for inhaled treatment Worsening respiration, bacterial pneumonia, and pneumothorax reported; rarely non-specific anaemia and haemolysis

Specific side-effects for oral treatment Haemolytic anaemia (anaemia may be improved by epoetin); also (in combination with peginterferon alfa or interferon alfa) nausea, vomiting, dyspepsia, abdominal pain, flatulence, constipation, diarrhoea, colitis, chest pain, palpitation, tachycardia, peripheral oedema, changes in blood pressure, syncope, flushing, pallor, cough, dyspnoea, tachypnoea, headache, dizziness, hyperkinesia, asthenia, impaired concentration and memory, sleep disturbances, abnormal dreams, anxiety, depression, suicidal ideation, psychoses, dysphagia, weight loss, dysphonia, paraesthesia, hypoaesthesia, ataxia, hypertension, influenza-like symptoms, growth retardation (including decrease in height and weight), thyroid disorders, hyperglycaemia, menstrual disturbances, virilism, breast pain, testicular pain, sexual dysfunction, micturition disorders, leucopenia, thrombocytopenia, lymphadenopathy, dehydration, hypocalcaemia, myalgia, arthralgia, hyperuricaemia, visual disturbances, eye pain, dry eyes, hearing impairment, tinnitus, earache, dry mouth, taste disturbances, mouth ulcers, stomatitis, glossitis, tooth disorder, gingivitis, alopecia, pruritus, dry skin, skin discoloration, rash (including very rarely Stevens-Johnson

syndrome and toxic epidermal necrolysis), increased sweating, psoriasis, photosensitivity, and acne; *less commonly* pancreatitis, gastro-intestinal bleeding, and hypertriglyceridaemia; *rarely* peptic ulcer, arrhythmias, cardiomyopathy, myocardial infarction, pericarditis, stroke, interstitial pneumonitis, pulmonary embolism, seizures, renal failure, vasculitis, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, optic neuropathy, and retinal haemorrhage; *very rarely* aplastic anaemia and peripheral ischaemia

Licensed use inhalation licensed for use in children (age range not specified by manufacturer); intravenous preparation not licensed

Indications and dose

Bronchiolitis

- By aerosol inhalation or nebulisation (via small particle aerosol generator)

Child 1 month–2 years inhale solution containing 20 mg/mL for 12–18 hours for at least 3 days; max. 7 days

Life-threatening RSV, parainfluenza virus, and adenovirus infection in immunocompromised children (seek expert advice)

- By intravenous infusion over 15 minutes

Child 1 month–18 years 33 mg/kg as a single dose, then 16 mg/kg every 6 hours for 4 days, then 8 mg/kg every 8 hours for 3 days

Chronic hepatitis C (in combination with interferon alfa or peginterferon alfa) in previously untreated children without liver decompensation

- By mouth

Child over 3 years; body-weight under 47 kg 15 mg/kg daily in 2 divided doses

Child body-weight 47–50 kg 200 mg in the morning and 400 mg in the evening

Child body-weight 50–65 kg 400 mg twice daily

Child body-weight 65–81 kg 400 mg in the morning and 600 mg in the evening

Child body-weight 81–105 kg 600 mg twice daily


Child body-weight over 105 kg 600 mg in the morning and 800 mg in the evening

Rebetol® (MSD) (PoM)

Capsules, ribavirin 200 mg, net price 84-cap pack = £160.90, 140-cap pack = £267.81, 168-cap pack = £321.38. Label: 21

Oral solution, ribavirin 200 mg/5 mL, net price 100 mL (bubble-gum-flavoured) = £67.08. Label: 21

Virazole® (Meda) (PoM)

Inhalation , ribavirin 6 g for reconstitution with 300 mL water for injections. Net price 3 × 6-g vials = £349.00

Intravenous infusion, 100 mg/mL, 10-mL amp Available on a named-patient basis from Valeant

5.4 Antiprotozoal drugs

- 5.4.1 Antimalarials
- 5.4.2 Amoebicides
- 5.4.3 Trichomonacides
- 5.4.4 Anti-giardial drugs
- 5.4.5 Leishmaniacides
- 5.4.6 Trypanocides
- 5.4.7 Drugs for toxoplasmosis
- 5.4.8 Drugs for pneumocystis pneumonia

Advice on specific problems available from:

Advice for healthcare professionals	
PHE (Public Health England) Malaria Reference Laboratory	(020) 7637 0248 (Fax)
www.malaria-reference.co.uk	(prophylaxis only)
National Travel Health Network and Centre	0845 602 6712
Travel Medicine Team, Health Protection, Scotland (registered users of Travax only)	(0141) 300 1100 (weekdays 2–4 p.m. only)
www.travax.nhs.uk (for registered users of the NHS Travax website only)	
Birmingham	(0121) 424 0357
Liverpool	(0151) 705 3100
London	0845 155 5000 (treatment)
Oxford	(01865) 225 430
Advice for travellers	
Hospital for Tropical Diseases, Travel Healthline	020 7950 7799
www.fitfortravel.nhs.uk	
WHO advice on international travel and health	
www.who.int/ith	
National Travel Health Network and Centre (NaTHNaC)	
www.nathnac.org/travel/index.htm	

Quinine, Malarone® (proguanil with atovaquone), or **Riamet®** (artemether with lumefantrine) can be given *by mouth* if the child can swallow and retain tablets and there are no serious manifestations (e.g. impaired consciousness); quinine should be given *by intravenous infusion* (see below) if the child is seriously ill or unable to take tablets. **Mefloquine** is now rarely used for treatment because of concerns about resistance.

Oral. Quinine is well tolerated by children although the salts are bitter.

The dosage regimen for quinine *by mouth* is:
10 mg/kg (of quinine salt¹; max. 600 mg) every 8 hours for 7 days
together with or followed by
either **clindamycin** 7–13 mg/kg (max. 450 mg) every 8 hours for 7 days [unlicensed indication]
or, in children over 12 years, **doxycycline** 200 mg once daily for 7 days

If the parasite is likely to be sensitive, **pyrimethamine** with **sulfadoxine** as a single dose [unlicensed] may be given (instead of either clindamycin or doxycycline) together with, or after, a course of quinine.

The dose regimen for pyrimethamine with sulfadoxine *by mouth* is:

Child up to 4 years and body-weight over 5 kg pyrimethamine 12.5 mg with sulfadoxine 250 mg as a single dose

Child 5–6 years pyrimethamine 25 mg with sulfadoxine 500 mg as a single dose

Child 7–9 years pyrimethamine 37.5 mg with sulfadoxine 750 mg as a single dose

Child 10–14 years pyrimethamine 50 mg with sulfadoxine 1 g as a single dose

Child 14–18 years pyrimethamine 75 mg with sulfadoxine 1.5 g as a single dose

Alternatively, **Malarone®**, or **Riamet®** may be given instead of quinine. It is not necessary to give clindamycin, doxycycline, or pyrimethamine with sulfadoxine after **Malarone®** or **Riamet®** treatment.

The dose regimen for **Malarone®** *by mouth* is:

Child body-weight 5–9 kg 2 'paediatric' tablets once daily for 3 days

Child body-weight 9–11 kg 3 'paediatric' tablets once daily for 3 days

Child body-weight 11–21 kg 1 'standard' tablet once daily for 3 days

Child body-weight 21–31 kg 2 'standard' tablets once daily for 3 days

Child body-weight 31–40 kg 3 'standard' tablets once daily for 3 days

Child body-weight over 40 kg 4 'standard' tablets once daily for 3 days

The dose regimen for **Riamet®** *by mouth* is:

Child body-weight 5–15 kg 1 tablet initially, followed by 5 further doses of 1 tablet each given at 8, 24, 36, 48, and 60 hours (total 6 tablets over 60 hours)

Child body-weight 15–25 kg 2 tablets initially, followed by 5 further doses of 2 tablets each given at

1. Valid for quinine hydrochloride, dihydrochloride, and sulfate; not valid for quinine bisulfate which contains a correspondingly smaller amount of quinine.

5.4.1 Antimalarials

Recommendations on the prophylaxis and treatment of malaria reflect guidelines agreed by UK malaria specialists. Choice will depend on the age of the child (see below).

The centres listed above should be consulted for advice on special problems.

Treatment of malaria

If the infective species is **not known**, or if the infection is **mixed**, initial treatment should be as for *falciparum malaria* with quinine, **Malarone®** (proguanil with atovaquone), or **Riamet®** (artemether with lumefantrine). *Falciparum malaria* can progress rapidly in unprotected children and antimalarial treatment should be considered in those with features of severe malaria and possible exposure, even if the initial blood tests for the organism are negative.

Falciparum malaria (treatment)

Falciparum malaria (malignant malaria) is caused by *Plasmodium falciparum*. In most parts of the world *P. falciparum* is now resistant to chloroquine which should not therefore be given for treatment.

8, 24, 36, 48, and 60 hours (total 12 tablets over 60 hours)

Child body-weight 25–35 kg 3 tablets initially, followed by 5 further doses of 3 tablets each given at 8, 24, 36, 48, and 60 hours (total 18 tablets over 60 hours)

Child 12–18 years and body-weight over 35 kg, 4 tablets initially followed by 5 further doses of 4 tablets each given at 8, 24, 36, 48, and 60 hours (total 24 tablets over 60 hours)

Parenteral. If the child is seriously ill or unable to swallow tablets, or if more than 2% of red blood cells are parasitized, **quinine** should be given by *intravenous infusion*. The dose regimen for quinine by *intravenous infusion* is calculated on a mg/kg basis:

Neonates and children, loading dose^{1,2} of 20 mg/kg (up to maximum 1.4 g) of quinine salt³ infused over 4 hours *then 8 hours after the start of the loading dose*, maintenance dose of 10 mg/kg⁴ (up to maximum 700 mg) of quinine salt³ infused over 4 hours every 8 hours (until child can swallow tablets to complete the 7-day course *together with or followed by either* clindamycin or doxycycline as above).

Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine, infection acquired in quinine-resistant areas of south-east Asia) because intravenous **artesunate** may be available for 'named-patient' use.

Pregnancy Falciparum malaria is particularly dangerous in pregnancy, especially in the last trimester. The treatment doses of oral and intravenous quinine given above (including the loading dose) can safely be given in pregnancy. Clindamycin [unlicensed indication] should be given for 7 days with or after quinine. Doxycycline should be avoided in pregnancy (affects teeth and skeletal development in fetus); pyrimethamine with sulfadoxine, **Malarone**[®], and **Riamet**[®] are also best avoided until more information is available. Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine, infection acquired in quinine-resistant areas of south east Asia) because intravenous artesunate may be available for 'named patient' use.

Non-falciparum malaria (treatment)

Non-falciparum malaria is usually caused by *Plasmodium vivax* and less commonly by *P. ovale* and *P. malariae*. *P. knowlesi* is also present in the Asia-Pacific region. **Chloroquine**⁵ is the drug of choice for the treatment of non-falciparum malaria (but chloroquine-resistant *P. vivax* has been reported in the Indonesian

archipelago, the Malay Peninsula, including Myanmar, and eastward to southern Vietnam).

Chloroquine alone is adequate for *P. malariae* and *P. knowlesi* infections but in the case of *P. vivax* and *P. ovale*, a **radical cure** (to destroy parasites in the liver and thus prevent relapses) is required. This is achieved with **primaquine**⁶ given after the chloroquine.

The dosage regimen of chloroquine *by mouth* for non-falciparum malaria in children is:

initial dose of 10 mg/kg of base (max. 620 mg) *then*

a single dose of 5 mg/kg of base (max. 310 mg) after 6–8 hours *then*

a single dose of 5 mg/kg of base (max. 310 mg) daily for 2 days

For a **radical cure**, **primaquine**⁶ [unlicensed] is then given to children over 6 months of age; specialist advice should be sought for children under 6 months of age. Primaquine is given in a dose of 250 micrograms/kg (max. 15 mg) daily for 14 days in *P. ovale* infection or 500 micrograms/kg (max. 30 mg) daily for 14 days in *P. vivax* infection.

Parenteral If the child is unable to take oral therapy, quinine can be given by *intravenous infusion*. The dose is 10 mg/kg⁴ (max. 700 mg) of quinine salt³ infused over 4 hours every 8 hours, changed to oral chloroquine as soon as the child's condition permits.

Pregnancy Treatment doses of chloroquine can be given for non-falciparum malaria. In the case of *P. vivax* or *P. ovale*, however, the radical cure with primaquine should be **postponed** until the pregnancy is over; instead chloroquine should be continued at a dose of 10 mg/kg (max. 310 mg) each week during the pregnancy.

Prophylaxis against malaria

The recommendations on prophylaxis reflect guidelines agreed by UK malaria specialists; the advice is aimed at residents of the UK who travel to endemic areas. The choice of drug for a particular child should take into account:

- risk of exposure to malaria;
- extent of drug resistance;
- efficacy of the recommended drugs;
- side-effects of the drugs;
- patient-related factors (e.g. age, pregnancy, renal or hepatic impairment, compliance with prophylactic regimen).

Prophylactic doses are based on guidelines agreed by UK malaria experts and may differ from advice in product literature. **Weight is a better guide than age.** If in doubt obtain advice from specialist centre, see p. 334.

Protection against bites **Prophylaxis is not absolute**, and breakthrough infection can occur with any of the drugs recommended. Personal protection against

1. In intensive care units the loading dose can alternatively be given as quinine salt³ 7 mg/kg infused over 30 minutes followed immediately by 10 mg/kg over 4 hours *then* (after 8 hours) maintenance dose as described.
2. **Important:** the loading dose of 20 mg/kg should **not** be used if the patient has received quinine or mefloquine during the previous 12 hours
3. Valid for quinine hydrochloride, dihydrochloride, and sulfate; not valid for quinine bisulfate which contains a correspondingly smaller amount of quinine.
4. Maintenance dose should be reduced to 5–7 mg/kg of quinine salt³ in children with severe renal impairment, severe hepatic impairment, or if parenteral treatment is required for more than 48 hours.
5. For the treatment of chloroquine-resistant non-falciparum malaria, **Malarone**[®] [unlicensed indication], quinine, or **Riamet**[®] [unlicensed indication] can be used; as with chloroquine, primaquine should be given for radical cure.

being bitten is very important. Mosquito nets impregnated with permethrin provide the most effective barrier protection against insects (infants should sleep with a mosquito net stretched over the cot or baby carrier); mats and vapourised insecticides are also useful. Diethyltoluamide (DEET) 20–50% in lotions, sprays, or roll-on formulations is safe and effective when applied to the skin of adults and children over 2 months of age. It can also be used during pregnancy and breast-feeding. The duration of protection varies according to the concentration of DEET and is longest for DEET 50%. When sunscreen is also required, DEET should be applied after the sunscreen. Long sleeves and trousers worn after dusk also provide protection against bites.

Length of prophylaxis In order to determine tolerance and to establish habit, prophylaxis should generally be started one week (2–3 weeks in the case of mefloquine) before travel into an endemic area; *Malarone*® or doxycycline prophylaxis should be started 1–2 days before travel. Prophylaxis should be continued for **4 weeks after leaving** (except for *Malarone*® prophylaxis which should be stopped 1 week after leaving).

In those requiring long-term prophylaxis, chloroquine and proguanil may be used for periods of over 5 years. Mefloquine is licensed for use up to 1 year (although, if it is tolerated in the short term, there is no evidence of harm when it is used for up to 3 years). Doxycycline can be used for up to 2 years. *Malarone*® can be used for up to 1 year. Prophylaxis with mefloquine, doxycycline, or *Malarone*® may be considered for longer durations if it is justified by the risk of exposure to malaria. Specialist advice should be sought for long-term prophylaxis.

Return from malarial region It is important to be aware that **any illness** that occurs within 1 year and **especially within 3 months of return might be malaria** even if all recommended precautions against malaria were taken. Travellers and carers of children should be **warned** of this and told that if they develop any illness **particularly within 3 months** of their return they should go **immediately** to a doctor and specifically mention their exposure to malaria.

Epilepsy Both chloroquine and mefloquine are unsuitable for malaria prophylaxis in children with a history of epilepsy. In areas *without chloroquine resistance*, proguanil alone is recommended; in areas *with chloroquine resistance*, doxycycline or *Malarone*® may be considered. The metabolism of doxycycline may be influenced by antiepileptics (see **interactions**: Appendix 1 (tetracyclines)).

Asplenia Asplenic children (or those with severe splenic dysfunction) are at particular risk of severe malaria. If travel to malarious areas is unavoidable, rigorous precautions are required against contracting the disease.

Renal impairment Avoidance (or dosage reduction) of proguanil is recommended since it is excreted by the kidneys. *Malarone*® should not be used for prophylaxis in children with estimated glomerular filtration rate less than 30 mL/minute/1.73 m². Chloroquine is only partially excreted by the kidneys and reduction of the dose for prophylaxis is not required except in severe impairment. Mefloquine is considered to be appropriate to use in renal impairment and does not require dosage reduction. Doxycycline is also considered to be appropriate.

Pregnancy Travel to malarious areas should be avoided during pregnancy; if travel is unavoidable,

effective prophylaxis must be used. Chloroquine and proguanil can be given in the usual doses during pregnancy, but these drugs are not appropriate for most areas because their effectiveness has declined, particularly in sub-Saharan Africa; in the case of proguanil, folic acid 5 mg daily should be given for at least the first trimester. The centres listed on p. 334 should be consulted for advice on prophylaxis in chloroquine-resistant areas. Although the manufacturer advises that mefloquine should not be used during pregnancy, particularly in the first trimester, unless the potential benefit outweighs the risk, studies of mefloquine in pregnancy (including use in the first trimester) indicate that it can be considered for travel to chloroquine-resistant areas. Doxycycline is contra-indicated during pregnancy (see section 5.1.3); however, it can be used for malaria prophylaxis if other regimens are unsuitable, and if the entire course of doxycycline can be completed before 15 weeks' gestation [unlicensed]. *Malarone*® should be avoided during pregnancy, however, it can be considered during the second and third trimesters if there is no suitable alternative.

Breast-feeding Prophylaxis is required in **breast-fed infants**; although antimalarials are present in milk, the amounts are too variable to give reliable protection.

Anticoagulants Travellers taking warfarin should begin chemoprophylaxis 2–3 weeks before departure. The INR should be stable before departure. It should be measured before starting chemoprophylaxis, 7 days after starting, and after completing the course. For prolonged stays, the INR should be checked at regular intervals.

Specific recommendations

Where a journey requires two regimens, the regimen for the higher risk area should be used for the whole journey. Those travelling to remote or little-visited areas may require expert advice.

Important

Settled immigrants (or long-term visitors) to the UK may be unaware that **any immunity they may have acquired while living in malarious areas is lost rapidly** after migration to the UK, or that any non-malarious areas where they lived previously **may now be malarious**

Key to recommended regimens for prophylaxis against malaria

Codes for regimens	Details of regimens for prophylaxis against malaria
1	Chemoprophylaxis not recommended, but avoid mosquito bites and consider malaria if fever presents
2	Chloroquine only
3	Chloroquine + proguanil hydrochloride
4	<i>Malarone</i> ® or doxycycline or mefloquine
5	<i>Malarone</i> ® or doxycycline

Specific recommendations: Afghanistan–Burundi

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
Afghanistan	Risk below 2000 m from May–November	3
	Low to no risk above 2000 m	1
Algeria	Very low risk in Illizi department only	1
Andaman and Nicobar Islands (India)	Risk present	3
Angola	High risk	4
Argentina	Low risk in low altitude areas of Salta provinces bordering Bolivia and in Chaco, Corrientes, and Misiones provinces close to border with Paraguay and Brazil	2
	No risk in areas other than those above and Iguazu Falls	1
Azerbaijan	Low to no risk	1
Bahamas	Sporadic local transmission on Great Exuma Island only	1
Bangladesh	High risk in Chittagong Hill Tract districts (but not Chittagong city)	4
	Low to no risk in Chittagong city and other areas, except Chittagong Hill Tract districts	1
Belize	Low risk in rural areas	2
Benin	High risk	4
Bhutan	Risk in southern belt districts, along border with India: Chukha, Geyleg-phug, Samchi, Samdrup Jonkhar, and Shemgang	3
	Low to no risk in areas other than those above	1
Bolivia	High risk in Amazon basin	4
	Risk in rural areas below 2500 m (other than above)	2
	No risk above 2500 m	1
Botswana	High risk from November–June in northern half, including Okavango Delta area	4
	Low to no risk in southern half	1
Brazil	Risk in Amazon basin, including city of Manaus	4
	Very low risk in areas other than those above, and no risk in Iguazu Falls	1
Brunei Darussalam	Very low risk	1
Burkina Faso	High risk	4
Burundi	High risk	4

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Specific recommendations: Cambodia–Ethiopia

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
Cambodia	High risk, with widespread chloroquine and mefloquine resistance, in western provinces bordering Thailand	5
	High risk in areas other than those above and below	4
	Very low risk in Angkor Wat and Lake Tonle Sap; no risk in Phnom Penh	1
Cameroon	High risk	4
Cape Verde	Very low risk on island of Santiago (Sao Tiago) and Boa Vista	1
Central African Republic	High risk	4
Chad	High risk	4
China	High risk in Yunnan and Hainan provinces	4
	Very low risk in areas other than those above and below	1
	No risk in Hong Kong	–
Colombia	High risk in rural areas below 1600 m	4
	Low to no risk above 1600 m and in Cartagena	1
Comoros	High risk	4
Congo	High risk	4
Costa Rica	Risk in Limon province (but not city of Limon)	2
	Very low risk in other areas than those above	1
Cote d'Ivoire (Ivory Coast)	High risk	4
Democratic Republic of the Congo	High risk	4
Djibouti	High risk	4
Dominican Republic	Risk in all areas except cities of Santiago and Santo Domingo	2
	Cities of Santiago and Santo Domingo	1
East Timor (Timor-Leste)	High risk	4
Ecuador	Risk in areas below 1500 m including coastal provinces and Amazon basin (no risk in Galapagos islands or city of Guayaquil)	4
El Salvador	Low risk in rural areas of Santa Ana, Ahuachapán, and La Unión provinces in western part of country; low to no risk in other areas	1
Equatorial Guinea	High risk	4
Eritrea	High risk below 2200 m	4
Ethiopia	High risk below 2000 m	4

Specific recommendations: French Guiana–Jamaica

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
French Guiana	High risk, particularly in border areas (no risk in city of Cayenne or Devil's Island (Ile du Diable))	4
Gabon	High risk	4
Gambia	High risk	4

Specific recommendations: French Guiana–Jamaica (continued)

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
Georgia	Very low risk in rural south east from June–October	1
Ghana	High risk	4
Guatemala	Low risk below 1500 m	2
	No risk in Guatemala City, Antigua, or Lake Atitlán	–
Guinea	High risk	4
Guinea-Bissau	High risk	4
Guyana	High risk in all interior regions	4
	Very low risk in Georgetown and coastal region	1
Haiti	Risk present	2
Honduras	Risk below 1000 m and in Roatán and other Bay Islands (no risk in San Pedro Sula or Tegucigalpa)	2
India	High risk in Assam	4
	Risk in Goa, Andaman and Nicobar islands, and areas other than those above or below	3
	Very low risk in southern states of Kerala, Tamil Nadu, and Karnataka, southern Andhra Pradesh (including city of Hyderabad), Rajasthan (including city of Jaipur), Uttar Pradesh (including city of Agra), Punjab, the cities of Delhi, Kolkata, Mumbai (Bombay), Nagpur, Nasik, and Pune	1
	No risk in Lakshadweep islands	–
Indonesia	High risk in Lombok and Irian Jaya (Papua)	4
	Risk in areas other than those above or below	3
	Very low risk in Bali, and cities on islands of Java and Sumatra	1
	No risk in city of Jakarta	–
Indonesia (Borneo)	High risk	4
Iran	Risk from March–November in rural south eastern provinces and in north, along Azerbaijan border in Ardabil, and near Turkmenistan border in North Khorasan	3
	Low to no risk in areas other than those above	–
Iraq	Very low risk from May–November in rural northern area below 1500 m	1
Jamaica	Sporadic local transmission reported in Kingston; no risk in other areas	1

Specific recommendations: Kenya–Myanmar

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
Kenya	High risk below 2500 m (except city of Nairobi)	4
	Very low risk above 2500 m and in city of Nairobi	1
Kyrgyzstan	Very low risk from June–October in southwest areas bordering Tajikistan and Uzbekistan	1
Laos	High risk along the border with Myanmar in the provinces of Bokeo and Louang Namtha, and along the border with Thailand in the province of Champasak and Saravan	5
	High risk in areas other than those above or below	4
	Low to no risk in city of Vientiane	1
Liberia	High risk	4
Madagascar	High risk	4
Malawi	High risk	4
Malaysia	Risk in inland forested areas of peninsular Malaysia	4
	Very low risk in rest of peninsular Malaysia, including Cameron Highlands and city of Kuala Lumpur	1
Malaysia (Borneo)	High risk in inland areas of eastern Sabah and in inland, forested areas of Sarawak	4
	Very low risk in areas other than those above, including coastal areas of Sabah and Sarawak	1
Mali	High risk	4

Specific recommendations: Kenya–Myanmar (continued)

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
Mauritania	High risk all year in southern provinces, and from July–October in the north	4
	Low to no risk in areas other than those above	1
Mayotte	Risk present	4
Mexico	Low risk in Oaxaca and Chiapas	2
	Very low risk in areas other than those above	1
Mozambique	High risk	4
Myanmar	High risk (but not in cities of Mandalay and Yangon)	5
	No risk in cities of Mandalay and Yangon	1

Key to recommended regimens for prophylaxis against malaria

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5	<i>Malarone</i> ® or doxycycline

Specific recommendations: Namibia–Rwanda

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
Namibia	High risk all year in regions of Caprivi Strip, Kavango, and Kunene river, and from November–June in northern third of country	4
	Low to no risk in areas other than those above	1
Nepal	Risk below 1500 m, particularly in Terai district	3
	No risk in city of Kathmandu and on typical Himalayan treks	1
Nicaragua	Low risk (except Managua)	2
	Very low risk in Managua	1
Niger	High risk	4
Nigeria	High risk	4
North Korea	Very low risk in some southern areas	1
Oman	Sporadic local transmission reported subsequent to international importation	1
Pakistan	Risk below 2000 m	3
	Low to no risk above 2000 m	1
Panama	Risk east of Canal Zone	3
	Low risk west of Canal Zone	2
	No risk in Panama City or Canal Zone itself	1
Papua New Guinea	High risk below 1800 m	4
	Low to no risk above 1800 m	1
Paraguay	Low risk in departments of Alto Paraná and Caaguazú	2
	Very low risk in areas other than those above	1
Peru	High risk in Amazon basin along border with Brazil, particularly in Loreto province	4
	Risk in rural areas below 2000 m (other than those above and below) and in part of the Amazon basin that borders Bolivia	2
	No risk in city of Lima and coastal region south of Chiclayo	–
Philippines	Risk in rural areas below 600 m and on islands of Luzon, Mindanao, Mindoro, and Palawan	3
	No risk in cities or on islands of Boracay, Bohol, Catanduanes, Cebu, or Leyte	1
Rwanda	High risk	4

Specific recommendations: São Tomé and Príncipe–Syria

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
São Tomé and Príncipe	High risk	4
Saudi Arabia	Risk in south-western provinces along border with Yemen, including below 2000 m in Asir province	3
	No risk in cities of Jeddah, Makkah (Mecca), Medina, Riyadh, or Ta'if, or above 2000 m in Asir province	1
Senegal	High risk	4
Sierra Leone	High risk	4
Solomon Islands	High risk	4
Somalia	High risk	4
South Africa	High risk in north-east KwaZulu-Natal, as far south as Tugela river, and in low altitude areas of Mpumalanga and Limpopo, which border Mozambique and Zimbabwe (including Kruger National Park)	4
	Low risk in areas bordering those above	1
South Korea	Very low risk in northern areas, in Gangwon-do and Gyeonggi-do provinces, and Incheon city (towards Demilitarized Zone)	1
South Sudan	High risk	4
Sri Lanka	Risk north of Vavuniya	3
	Low to no risk in areas other than those above and below	1
	No risk in Colombo or Kandy	–
Sudan	High risk in central and southern areas; risk also present in rest of country (except Khartoum)	4
	Very low risk in Khartoum	1
Suriname	High risk (except coastal districts or city of Paramaribo)	4
	Very low risk in coastal districts; no risk in city of Paramaribo	1
Swaziland	High risk in northern and eastern regions bordering Mozambique and South Africa, including all of Lubombo district and Big Bend, Mhlume, Simunye, and Tshaneni regions	4
	Very low risk in the west	1
Syria	Very low risk in small remote foci of Al Hasakah	1

Specific recommendations: Tajikistan–Zimbabwe

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
Tajikistan	Risk below 2000 m from June–October	3
Tanzania	High risk below 1800 m; risk also in Zanzibar	4
Thailand	High risk, with chloroquine and mefloquine resistance, in rural forested borders with Cambodia, Laos, and Myanmar	5
	Very low risk in areas other than those above, including Kanchanaburi (Kwai Bridge); no risk in cities of Bangkok, Chiang Mai, Chiang Rai, Koh Phangan, Koh Samui, and Pattaya	1
Togo	High risk	4
Turkey	Low risk from May–October along the border plain with Syria, around Adana and east of Adana	2
	Very low risk in areas other than those above	1
Uganda	High risk	4
Uzbekistan	Very low risk in extreme south-east	1
Vanuatu	Risk present	4
Venezuela	High risk in all areas south of, and including, the Orinoco river and Angel Falls	4
	Risk in rural areas of Apure, Monagas, Sucre, and Zulia states	3
	No risk in city of Caracas or on Margarita Island	1

Key to recommended regimens for prophylaxis against malaria

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4	<i>Malarone</i> ® or doxycycline or mefloquine
5	<i>Malarone</i> ® or doxycycline

Specific recommendations: Tajikistan–Zimbabwe (continued)

Country	Comments on risk of malaria and regional or seasonal variation	Codes for regimens
Vietnam	Risk in rural areas, and in southern provinces of Tay Ninh, Lam Dong, Dac Lac, Gia Lai, and Kon Tum	5
	Very low risk in Mekong river delta until border area with Cambodia; no risk in large cities (including Ho Chi Minh (Saigon) and Hanoi), Red river delta, and coastal areas north of Nha Trang	1
Yemen	Risk below 2000 m	3
	Very low risk on Socotra Island; no risk above 2000 m, including Sana'a city	1
Zambia	High risk	4
Zimbabwe	High risk all year in Zambezi valley, and from November–June in areas below 1200 m	4
	Very low risk in Harare and Bulawayo	1

Standby treatment [unlicensed]

Children and their carers visiting remote, malarious areas for prolonged periods should carry standby treatment if they are likely to be more than 24 hours away from medical care. Self-medication should be avoided if medical help is accessible.

In order to avoid excessive self-medication, the traveller should be provided with **written instructions** that urgent medical attention should be sought if fever (38°C or more) develops 7 days (or more) after arriving in a malarious area and that self-treatment is indicated if medical help is not available within 24 hours of fever onset.

In view of the continuing emergence of resistant strains and of the different regimens required for different areas expert advice should be sought on the best treatment course for an individual traveller. A drug used for chemoprophylaxis should not be considered for standby treatment for the same traveller.

Artemether with lumefantrine

Artemether with lumefantrine is licensed for the *treatment of acute uncomplicated falciparum malaria*.

ARTEMETHER WITH LUMEFANTRINE

Cautions electrolyte disturbances, concomitant use with other drugs known to cause QT-interval prolongation; monitor patients unable to take food (greater risk of recrudescence); avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (artemether with lumefantrine)

Skilled tasks Dizziness may affect performance of skilled tasks

Contra-indications history of arrhythmias, of clinically relevant bradycardia, and of congestive heart failure accompanied by reduced left ventricular ejection fraction; family history of sudden death or of congenital QT interval prolongation

Hepatic impairment manufacturer advises caution in severe impairment

Renal impairment manufacturer advises caution in severe impairment—monitor ECG and plasma potassium concentration

Pregnancy toxicity in animal studies with artemether; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid breast-feeding for at least 1 week after last dose; present in milk in animal studies

Side-effects abdominal pain, anorexia, diarrhoea, vomiting, nausea; palpitation, prolonged QT interval; cough; headache, dizziness, sleep disturbances, asthenia, paraesthesia; arthralgia, myalgia; pruritus, rash; *less commonly* ataxia, hypoaesthesia, clonus

Indications and dose

Treatment of acute uncomplicated falciparum malaria see p. 334

Treatment of non-falciparum malaria see p. 335

Administration tablets may be crushed just before administration

Riamet® (Novartis) (PoM)

Tablets, yellow, artemether 20 mg, lumefantrine 120 mg, net price 24-tab pack = £22.50. Label: 21, counselling, skilled tasks

Chloroquine

Chloroquine is used for the *prophylaxis of malaria* in areas of the world where the *risk of chloroquine-resistant falciparum malaria* is still low. It is also used with pro-

guanil when chloroquine-resistant falciparum malaria is present but this regimen may not give optimal protection (see specific recommendations by country, p. 337).

Chloroquine is **no longer recommended** for the treatment of falciparum malaria owing to widespread resistance, nor is it recommended if the infective species is *not known* or if the infection is *mixed*; in these cases treatment should be with quinine, *Malarone*®, or *Riamet*® (for details, see p. 334). It is still recommended for the treatment of non-falciparum malaria (for details, see p. 335).

CHLOROQUINE

Cautions may exacerbate psoriasis, neurological disorders (avoid for prophylaxis if history of epilepsy, see notes above), may aggravate myasthenia gravis, severe gastro-intestinal disorders, G6PD deficiency (see section 9.1.5); ophthalmic examination with long-term therapy; avoid concurrent therapy with hepatotoxic drugs—other **interactions**: Appendix 1 (chloroquine and hydroxychloroquine)

Hepatic impairment use with caution in moderate to severe impairment

Renal impairment manufacturers advise caution; see also Prophylaxis Against Malaria, p. 336

Pregnancy benefit of prophylaxis and treatment in malaria outweighs risk; see also Non-falciparum Malaria (treatment), p. 335 and Prophylaxis Against Malaria, p. 336

Breast-feeding amount in milk probably too small to be harmful; see also Prophylaxis Against Malaria, p. 336

Side-effects gastro-intestinal disturbances, headache, skin reactions (rashes, pruritus); also hypotension, diffuse parenchymal lung disease, convulsions, extrapyramidal symptoms, visual disturbances, depigmentation or loss of hair, drug rash with eosinophilia and systemic symptoms; rarely bone-marrow suppression, hypersensitivity reactions such as urticaria and angioedema; other side-effects (not usually associated with malaria prophylaxis or treatment), see under hydroxychloroquine side-effects in Antimalarials, section 10.1.3; very toxic in **overdose**—immediate advice from poisons centres essential (see also p. 28)

Indications and dose

Prophylaxis of malaria

• By mouth

Dose (expressed as chloroquine base) started 1 week before entering endemic area and continued for 4 weeks after leaving (see notes above)

Child up to 6 weeks, body-weight under 4.5 kg 25 mg once weekly

Child 6 weeks–6 months, body-weight 4.5–8 kg 50 mg once weekly

Child 6 months–1 year, body-weight 8–11 kg 75 mg once weekly

Child 1–3 years, body-weight 11–15 kg 100 mg once weekly

Child 3–4 years, body-weight 15–16.5 kg 125 mg once weekly

Child 4–8 years, body-weight 16.5–25 kg 150 mg once weekly (or 155 mg once weekly if tablets used)

Child 8–13 years, body-weight 25–45 kg 225 mg once weekly (or 232.5 mg once weekly if tablets used)

Child over 13 years, body-weight over 45 kg 310 mg once weekly

Counselling Warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return. For details, see notes above

Treatment of non-falciparum malaria see p. 335

Note Chloroquine doses in BNFC may differ from those in product literature

¹Avloclor® (Alliance) (PoM)

Tablets, scored, chloroquine phosphate 250 mg (= chloroquine base 155 mg). Net price 20-tab pack = £3.13. Label: 5, counselling, prophylaxis, see above

¹Malarivon® (Wallace Mfg) (PoM)

Syrup, chloroquine phosphate 80 mg/5 mL (= chloroquine base 50 mg/5 mL), net price 75 mL = £10.85. Label: 5, counselling, prophylaxis, see above

¹Nivaquine® (Sanofi-Aventis) (PoM)

Syrup, golden, chloroquine sulfate 68 mg/5 mL (= chloroquine base 50 mg/5 mL), net price 100 mL = £4.60. Label: 5, counselling, prophylaxis, see above

▲ With proguanil

For cautions and side-effects of proguanil see Proguanil; for dose see Chloroquine and Proguanil

¹Paludrine/Avloclor® (Alliance)

Tablets, travel pack of 14 tablets of chloroquine phosphate 250 mg (= chloroquine base 155 mg) and 98 tablets of proguanil hydrochloride 100 mg, net price 112-tab pack = £9.95. Label: 5, 21, counselling, prophylaxis, see above

Mefloquine

Mefloquine is used for the prophylaxis of malaria in areas of the world where there is a high risk of chloroquine-resistant falciparum malaria (for details, see specific recommendations by country, p. 337).

Mefloquine is now rarely used for the treatment of falciparum malaria because of increased resistance. It is rarely used for the treatment of non-falciparum malaria because better tolerated alternatives are available. Mefloquine should not be used for treatment if it has been used for prophylaxis.

MEFLOQUINE

Cautions cardiac conduction disorders; epilepsy (avoid for prophylaxis); traumatic brain injury; not recommended in infants under 3 months (5 kg); **interactions**: Appendix 1 (mefloquine)

Neuropsychiatric reactions Mefloquine is associated with potentially serious neuropsychiatric reactions. Abnormal dreams, insomnia, anxiety, and depression occur commonly. Psychosis, suicidal ideation, and suicide have also been reported. Psychiatric symptoms such as nightmares, acute anxiety, depression, restlessness, or confusion should be regarded as potentially prodromal for a more serious event. If neuropsychiatric symptoms occur, patients should be advised to discontinue mefloquine and to seek immediate

1. Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which anti-malarials are prescribed

medical attention so that mefloquine can be replaced with an alternative antimalarial. Adverse reactions may occur and persist up to several months after discontinuation because mefloquine has a long half-life. Mefloquine is contraindicated for malaria prophylaxis in those with a history of psychiatric disorders or convulsions

Skilled tasks Dizziness or a disturbed sense of balance may affect performance of skilled tasks; effects may occur and persist up to several months after stopping mefloquine

Contra-indications hypersensitivity to quinine; history of blackwater fever; avoid for standby treatment if history of convulsions; avoid for prophylaxis if history of psychiatric disorders (including depression) or convulsions

Hepatic impairment elimination may be prolonged; avoid in severe impairment

Renal impairment manufacturer advises caution

Pregnancy manufacturer advises adequate contraception during prophylaxis and for 3 months after stopping (teratogenicity in *animal* studies), but see also p. 336

Breast-feeding present in milk but risk to infant minimal; see also, p. 336

Side-effects nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, visual disturbances, pruritus; see also Neuropsychiatric Reactions above; also reported anorexia, dyspepsia, hepatic failure, hypotension, hypertension, flushing, chest pain, bradycardia, tachycardia, palpitation, arrhythmias, syncope, oedema, dyspnoea, pneumonitis, drowsiness, sensory and motor neuropathies, tremor, ataxia, panic attacks, confusion, amnesia, seizures, encephalopathy, speech disturbances, malaise, fever, blood disorders (including leucopenia, leucocytosis, thrombocytopenia), muscle weakness, myalgia, arthralgia, cataract, optic neuropathy, vestibular disorders, rash (including Stevens-Johnson syndrome), alopecia, hyperhidrosis

Licensed use not licensed for use in children under 5 kg body-weight and under 3 months

Indications and dose

Prophylaxis of malaria started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving (see notes above)

• By mouth

Child body-weight 5–16 kg 62.5 mg once weekly

Child body-weight 16–25 kg 125 mg once weekly

Child body-weight 25–45 kg 187.5 mg once weekly

Child body-weight over 45 kg 250 mg once weekly

Long-term chemoprophylaxis Mefloquine prophylaxis can be taken for up to 1 year

Counselling Inform travellers and carers of children travelling about adverse reactions of mefloquine and, if they occur, to seek medical advice on alternative antimalarials before the next dose is due (see also Neuropsychiatric Reactions and Skilled Tasks above). Also warn travellers and carers of children travelling about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return. For details, see notes above

Note Mefloquine doses in BNFC may differ from those in product literature

Administration Tablet may be crushed and mixed with food such as jam or honey just before administration

1 Larium® (Roche) (PoM)

Tablets, scored, mefloquine (as hydrochloride) 250 mg. Net price 8-tab pack = £14.53. Label: 21, 27, counselling, skilled tasks, prophylaxis, see above

Piperaquine with arteminol

Piperaquine with arteminol is not recommended for the first-line treatment of acute uncomplicated falciparum malaria because there is limited experience of its use in travellers who usually reside in areas where malaria is not endemic. Piperaquine has a long half-life.

PIPERAQUINE PHOSPHATE WITH ARTEMINOL

(Piperaquine tetraphosphate with dihydroartemisinin)

Cautions obtain ECG as soon as possible after starting treatment then continue monitoring in those taking medicines that increase plasma-piperaquine concentration, in children who are vomiting, or in females; consider obtaining ECG in all patients before third dose and 4–6 hours after third dose; if QT_c interval more than 500 milliseconds, discontinue treatment and monitor ECG for a further 24–48 hours; **interactions:** Appendix 1 (piperaquine with arteminol)

Contra-indications risk factors for QT interval prolongation (e.g. electrolyte disturbances, acute myocardial infarction, severe hypertension, left ventricular hypertrophy, heart failure with reduced left ventricular ejection fraction, bradycardia, congenital long QT syndrome, family history of sudden death, concomitant use with other drugs known to prolong the QT interval, history of symptomatic arrhythmias)

Hepatic impairment no information available in moderate to severe impairment—manufacturer advises monitor ECG and plasma-potassium concentration

Renal impairment no information available in moderate to severe impairment—manufacturer advises monitor ECG and plasma-potassium concentration

Pregnancy teratogenic in *animal* studies—manufacturer advises use only if other antimalarials cannot be used

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects vomiting, abdominal pain, diarrhoea, QT interval prolonged, irregular heart rate, cough, malaise, blood disorders (including anaemia, leucopenia, and thrombocytopenia), conjunctivitis, rash; less commonly nausea, stomatitis, hepatitis, hepatomegaly, jaundice, arrhythmias, heart murmur, headache, convulsions, influenza-like symptoms, arthralgia, acanthosis

Indications and dose

Treatment of uncomplicated falciparum malaria see notes above and preparations

Eurartesim® (Sigma-Tau) ▼ (PoM)

Tablets, f/c, scored piperaquine phosphate 320 mg, arteminol 40 mg, net price 12-tab pack = £40.00.

Counselling, administration

Counselling Tablets to be taken at least 3 hours before and at least 3 hours after food. Tablets may be crushed and mixed with water immediately before administration

1. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed

Dose

Treatment of uncomplicated falciparum malaria

• By mouth

Child 6 months–18 years

Body-weight 7–13 kg ½ tablet once daily for 3 days

Body-weight 13–24 kg 1 tablet once daily for 3 days

Body-weight 24–36 kg 2 tablets once daily for 3 days

Body-weight 36–75 kg 3 tablets once daily for 3 days

Body-weight 75–100 kg 4 tablets once daily for 3 days

Note Max 2 courses in 12 months; second course given at least 2 months after first course

Primaquine

Primaquine is used to eliminate the liver stages of *P. vivax* or *P. ovale* following chloroquine treatment (for details, see p. 335).

PRIMAQUINE

Cautions G6PD deficiency (test blood, see under Non-falciparum Malaria (treatment), p. 335); systemic diseases associated with granulocytopenia (e.g. juvenile idiopathic arthritis, lupus erythematosus); **interactions:** Appendix 1 (primaquine)

Pregnancy risk of neonatal haemolysis and methaemoglobinaemia in third trimester; see also, p. 335

Breast-feeding no information available; theoretical risk of haemolysis in G6PD-deficient infants

Side-effects nausea, vomiting, anorexia, abdominal pain; less commonly methaemoglobinaemia, haemolytic anaemia especially in G6PD deficiency, leucopenia

Licensed use not licensed

Indications and dose

Adjunct in the treatment of *Plasmodium vivax* and *P. ovale* malaria (eradication of liver stages) for dose see Non-falciparum Malaria, p. 335

Primaquine (Non-proprietary)

Tablets, primaquine (as phosphate) 7.5 mg or 15 mg Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Proguanil

Proguanil is used (usually with chloroquine, but occasionally alone) for the prophylaxis of malaria, (for details, see specific recommendations by country, p. 337).

Proguanil used alone is not suitable for the treatment of malaria; however, Malarone® (a combination of atovaquone with proguanil) is licensed for the treatment of acute uncomplicated falciparum malaria.

Malarone® is also used for the prophylaxis of falciparum malaria in areas of widespread mefloquine or chloroquine resistance. Malarone® is also used as an alternative to mefloquine or doxycycline. Malarone® is particularly suitable for short trips to highly chloroquine-resistant areas because it needs to be taken only for 7 days after leaving an endemic area.

PROGUANIL HYDROCHLORIDE

Cautions interactions: Appendix 1 (proguanil)

Renal impairment (see notes under Prophylaxis against malaria). Use half normal dose if estimated glomerular filtration rate 20–60 mL/minute/1.73 m². Use one-quarter normal dose on alternate days if

estimated glomerular filtration rate 10–20 mL/minute/1.73 m². Use one-quarter normal dose once weekly if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²; increased risk of haematological toxicity.

Pregnancy benefit of prophylaxis in malaria outweighs risk; adequate folate supplements should be given to mother; see also p. 336

Breast-feeding amount in milk probably too small to be harmful when used for malaria prophylaxis; see also p. 336

Side-effects mild gastric intolerance, diarrhoea, and constipation; occasionally mouth ulcers and stomatitis; very rarely cholestasis, vasculitis, skin reactions and hair loss

Indications and dose

Prophylaxis of malaria started 1 week before entering endemic area and continued for 4 weeks after leaving (see notes above)

• By mouth

Child up to 12 weeks, body-weight under 6 kg 25 mg once daily

Child 12 weeks–1 year, body-weight 6–10 kg 50 mg once daily

Child 1–4 years, body-weight 10–16 kg 75 mg once daily

Child 4–8 years, body-weight 16–25 kg 100 mg once daily

Child 8–13 years, body-weight 25–45 kg 150 mg once daily

Child over 13 years, body-weight over 45 kg 200 mg once daily

Counselling Warn travellers and carers of children travelling about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return. For details, see notes above

Note Proguanil doses in BNFC may differ from those in product literature

Administration Tablets may be crushed and mixed with food such as milk, jam or honey just before administration

1 Paludrine® (Alliance)

Tablets, scored, proguanil hydrochloride 100 mg. Net price 98-tab pack = £8.65. Label: 21, counselling, prophylaxis, see above

■ With chloroquine

See under Chloroquine

PROGUANIL HYDROCHLORIDE WITH ATOVAQUONE

Cautions diarrhoea or vomiting (reduced absorption of atovaquone); efficacy not evaluated in cerebral or complicated malaria (including hyperparasitaemia, pulmonary oedema or renal failure); **interactions:** see Appendix 1 (proguanil, atovaquone)

Renal impairment avoid for malaria prophylaxis and, if possible, for treatment if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

1. Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials are prescribed

Pregnancy manufacturer advises avoid unless essential; see also p. 336

Breast-feeding use only if no suitable alternative available; see also Breast-feeding, p. 336

Side-effects abdominal pain, nausea, vomiting, diarrhoea; cough; headache, dizziness, insomnia, abnormal dreams, depression, anorexia, fever; rash, pruritus; *less frequently* stomatitis, palpitation, anxiety, blood disorders, hyponatraemia, and hair loss; also reported hepatitis, cholestasis, tachycardia, hallucinations, seizures, vasculitis, mouth ulcers, photosensitivity, Stevens-Johnson syndrome

Licensed use not licensed for prophylaxis of malaria in children under 11 kg; not licensed for treatment of non-falciparum malaria

Indications and dose

See Preparations

Counselling Warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return. For details, see Prophylaxis against malaria, above

¹Malarone® (GSK) (PoM)

Tablets ('standard'), pink, f/c, proguanil hydrochloride 100 mg, atovaquone 250 mg. Net price 12-tab pack = £25.21. Label: 21, counselling, prophylaxis, see above

Dose

Prophylaxis of malaria started 1–2 days before entering endemic area and continued for 1 week after leaving

• By mouth

Child body-weight over 40 kg 1 tablet daily

Treatment of malaria

• By mouth

Child body-weight 11–21 kg 1 tablet daily for 3 days

Child body-weight 21–31 kg 2 tablets once daily for 3 days

Child body-weight 31–40 kg 3 tablets once daily for 3 days

Child body-weight over 40 kg 4 tablets once daily for 3 days

¹Malarone® Paediatric (GSK) (PoM)

Paediatric tablets, pink, f/c proguanil hydrochloride 25 mg, atovaquone 62.5 mg, net price 12-tab pack = £6.26. Label: 21, counselling, prophylaxis, see above

Dose

Prophylaxis of malaria started 1–2 days before entering endemic area and continued for 1 week after leaving

• By mouth

Child body-weight 5–8 kg ½ tablet once daily

Child body-weight 8–10 kg ¾ tablet once daily

Child body-weight 10–20 kg 1 tablet once daily

Child body-weight 20–30 kg 2 tablets once daily

Child body-weight 30–40 kg 3 tablets once daily

Child body-weight over 40 kg use Malarone® ('standard') tablets, see above

Treatment of malaria

• By mouth

Child body-weight 5–9 kg 2 tablets once daily for 3 days

Child body-weight 9–11 kg 3 tablets once daily for 3 days

Child body-weight 11 kg and over use Malarone® ('standard') tablets, see above

Administration tablets may be crushed and mixed with food or milky drink just before administration

1. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed

Pyrimethamine

Pyrimethamine should not be used alone, but is used with sulfadoxine.

Pyrimethamine with sulfadoxine is not recommended for the *prophylaxis of malaria*, but can be used in the treatment of *falciparum malaria* with (or following) *quinine*.

PYRIMETHAMINE WITH SULFADOXINE

Cautions see under Pyrimethamine (section 5.4.7) and under Co-trimoxazole (section 5.1.8); not recommended for prophylaxis (severe side-effects on long-term use); **interactions:** Appendix 1 (pyrimethamine, sulfonamides)

Contra-indications see under Pyrimethamine (section 5.4.7) and under Co-trimoxazole (section 5.1.8); sulfonamide allergy

Pregnancy possible teratogenic risk in *first trimester* as pyrimethamine is a folate antagonist; in *third trimester*—risk of neonatal haemolysis and methaemoglobinemia; fear of increased risk of neonatal kernicterus appears unfounded; see also p. 335

Breast-feeding small risk of neonatal kernicterus in jaundiced infants; risk of haemolysis in G6PD-deficient child due to sulfadoxine

Side-effects see under Pyrimethamine (section 5.4.7) and under Co-trimoxazole (section 5.1.8); pulmonary infiltrates (e.g. eosinophilic or allergic alveolitis) reported—discontinue if cough or shortness of breath

Licensed use not licensed for use in children of body-weight under 5 kg

Indications and dose

Adjunct to quinine in treatment of *Plasmodium falciparum* malaria see p. 334

Prophylaxis not recommended by UK malaria experts

Pyrimethamine with sulfadoxine (Non-proprietary) (PoM)

Tablets, scored, pyrimethamine 25 mg, sulfadoxine 500 mg, net price 3-tab pack = 74p

Note Also known as *Fansidar*®

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Quinine

Quinine is not suitable for the *prophylaxis of malaria*.

Quinine is used for the *treatment of falciparum malaria* or if the infective species is *not known* or if the infection is *mixed* (for details see p. 334).

QUININE

Cautions cardiac disease (including atrial fibrillation, conduction defects, heart block)—monitor ECG during parenteral treatment; monitor blood glucose and electrolyte concentration during parenteral treatment; G6PD deficiency (see section 9.1.5); **interactions:** Appendix 1 (quinine)

Contra-indications haemoglobinuria, myasthenia gravis, optic neuritis, tinnitus

Hepatic impairment for treatment of malaria in severe impairment, reduce parenteral maintenance dose to 5–7 mg/kg of quinine salt

Renal impairment for treatment of malaria in severe impairment, reduce parenteral maintenance dose to 5–7 mg/kg of quinine salt

Pregnancy risk of teratogenesis with high doses in *first trimester*; but in malaria benefit of treatment outweighs risk, see also p. 335

Breast-feeding present in milk but not known to be harmful

Side-effects cinchonism, including tinnitus, hearing impairment, vertigo, headache, nausea, vomiting, abdominal pain, diarrhoea, visual disturbances (including temporary blindness); agitation, confusion; cardiovascular effects (see Cautions); dyspnoea; hypersensitivity reactions including angioedema, rashes, hot and flushed skin; hypoglycaemia (especially after parenteral administration); blood disorders (including thrombocytopenia and intravascular coagulation); acute renal failure; muscle weakness; photosensitivity; very toxic in **overdosage**—immediate advice from poisons centres essential (see also p. 28)

Licensed use injection not licensed

Indications and dose

Treatment of malaria see p. 334

Note Quinine (anhydrous base) 100 mg = quinine bisulfate 169 mg = quinine dihydrochloride 122 mg = quinine hydrochloride 122 mg = quinine sulfate 121 mg. Quinine bisulfate 300-mg tablets are available but provide less quinine than 300 mg of the dihydrochloride, hydrochloride, or sulfate

Administration for *intravenous infusion*, dilute to a concentration of 2 mg/mL (max. 30 mg/mL in fluid restriction) with Glucose 5% or Sodium Chloride 0.9% and give over 4 hours

Quinine Sulfate (Non-proprietary) (PoM)

Tablets, coated, quinine sulfate 200 mg, net price 28-tab pack = £1.68; 300 mg, 28-tab pack = £1.80

Quinine Dihydrochloride (Non-proprietary) (PoM)

Injection, quinine dihydrochloride 300 mg/mL. For dilution and use as an infusion. 1- and 2-mL amps Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Note Intravenous injection of quinine is so hazardous that it has been superseded by infusion

Tetracyclines

Doxycycline (section 5.1.3) is used in children over 12 years for the *prophylaxis of malaria* in areas of *widespread mefloquine or chloroquine resistance*. Doxycycline is also used as an alternative to mefloquine or Malarone® (for details, see specific recommendations by country, p. 337).

Doxycycline is also used as an *adjunct to quinine in the treatment of falciparum malaria* (for details see p. 334).

DOXYCYCLINE

Cautions section 5.1.3

Contra-indications section 5.1.3

Hepatic impairment section 5.1.3

Renal impairment section 5.1.3

Pregnancy section 5.1.3

Breast-feeding section 5.1.3

Side-effects section 5.1.3

Licensed use not licensed for use in children under 12 years

Indications and dose

Prophylaxis of malaria preferably started 1–2 days before entering endemic area and continued for 4 weeks after leaving (see notes above)

• **By mouth**

Child over 12 years 100 mg once daily

Treatment of falciparum malaria see p. 334

Preparations

Section 5.1.3

5.4.2 Amoebicides

Metronidazole is the drug of choice for *acute invasive amoebic dysentery* since it is very effective against vegetative forms of *Entamoeba histolytica* which can cause ulceration of the large intestine. **Tinidazole** is also effective. Metronidazole and tinidazole are also active against amoebae which may have migrated to the liver. Treatment with metronidazole (or tinidazole) is followed by a 10-day course of diloxanide furoate.

Diloxanide furoate is the drug of choice for asymptomatic patients with *E. histolytica* cysts in the faeces; metronidazole and tinidazole are relatively ineffective. Diloxanide furoate is relatively free from toxic effects and the usual course is of 10 days, given alone for chronic infections or following metronidazole or tinidazole treatment.

For *amoebic abscesses* of the liver **metronidazole** is effective; tinidazole is an alternative. Aspiration of the abscess is indicated where it is suspected that it may rupture or where there is no improvement after 72 hours of metronidazole; the aspiration may need to be repeated. Aspiration aids penetration of metronidazole and, for abscesses with large volume of pus, if carried out in conjunction with drug therapy, may reduce the period of disability.

Diloxanide furoate is not effective against hepatic amoebiasis, but a 10-day course should be given at the completion of metronidazole or tinidazole treatment to destroy any amoebae in the gut.

DILOXANIDE FUROATE

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid

Side-effects flatulence, vomiting, urticaria, pruritus

Licensed use not licensed for use in children under 25 kg body-weight

Indications and dose

Chronic amoebiasis and as adjunct to metronidazole or tinidazole in acute amoebiasis

• **By mouth**

Child 1 month–12 years 6.6 mg/kg 3 times daily for 10 days

Child 12–18 years 500 mg 3 times daily for 10 days

Diloxanide (Non-proprietary) (PoM)

Tablets, diloxanide furoate 500 mg, net price 30-tab pack = £93.50. Label: 9

METRONIDAZOLE

Cautions section 5.1.11

Hepatic impairment section 5.1.11

Pregnancy section 5.1.11

Breast-feeding section 5.1.11**Side-effects** section 5.1.11**Indications and dose****Anaerobic infections** section 5.1.11**Invasive intestinal amoebiasis, extra-intestinal amoebiasis (including liver abscess)**

• By mouth

Child 1–3 years 200 mg 3 times daily for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)**Child 3–7 years** 200 mg 4 times daily for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)**Child 7–10 years** 400 mg 3 times daily for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)**Child 10–18 years** 800 mg 3 times daily for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)**Urogenital trichomoniasis**

• By mouth

Child 1–3 years 50 mg 3 times daily for 7 days**Child 3–7 years** 100 mg twice daily for 7 days**Child 7–10 years** 100 mg 3 times daily for 7 days**Child 10–18 years** 200 mg 3 times daily for 7 days or 400–500 mg twice daily for 5–7 days, or 2 g as a single dose**Giardiasis**

• By mouth

Child 1–3 years 500 mg once daily for 3 days**Child 3–7 years** 600–800 mg once daily for 3 days**Child 7–10 years** 1 g once daily for 3 days**Child 10–18 years** 2 g once daily for 3 days or 400 mg 3 times daily for 5 days or 500 mg twice daily for 7–10 days■ **Preparations**

Section 5.1.11

TINIDAZOLE**Cautions** see under Metronidazole (section 5.1.11); avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (tinidazole)**Pregnancy** manufacturer advises avoid in first trimester**Breast-feeding** present in milk—manufacturer advises avoid breast-feeding during and for 3 days after stopping treatment**Side-effects** see under Metronidazole (section 5.1.11)**Licensed use** licensed for use in children (age range not specified by manufacturer)**Indications and dose****Intestinal amoebiasis**

• By mouth

Child 1 month–12 years 50–60 mg/kg (max. 2 g) once daily for 3 days**Child 12–18 years** 2 g once daily for 2–3 days**Amoebic involvement of liver**

• By mouth

Child 1 month–12 years 50–60 mg/kg (max. 2 g) once daily for 5 days**Child 12–18 years** 1.5–2 g once daily for 3–6 days**Urogenital trichomoniasis and giardiasis**

• By mouth

Child 1 month–12 years single dose of 50–75 mg/kg (max. 2 g) (repeated once if necessary)**Child 12–18 years** single dose of 2 g (repeated once if necessary)**Fasigyn[®]** (Pfizer) (POM)

Tablets, f/c, tinidazole 500 mg, net price 16-tablet pack = £11.04. Label: 4, 9, 21, 25

5.4.3 Trichomonacides**Metronidazole** (section 5.4.2) is the treatment of choice for *Trichomonas vaginalis* infection. Contact tracing is recommended and sexual contacts should be treated simultaneously. If metronidazole is ineffective, **tinidazole** (section 5.4.2) may be tried.**5.4.4 Anti giardial drugs****Metronidazole** (section 5.4.2) is the treatment of choice for *Giardia lamblia* infections. **Tinidazole** (section 5.4.2) may be used as an alternative to metronidazole.**5.4.5 Leishmaniacides**

Cutaneous leishmaniasis frequently heals spontaneously but if skin lesions are extensive or unsightly, treatment is indicated, as it is in visceral leishmaniasis (kala-azar). Leishmaniasis should be treated under specialist supervision.

Sodium stibogluconate, an organic pentavalent antimony compound, is the treatment of choice for visceral leishmaniasis. The dose is 20 mg/kg daily for at least 20 days by intramuscular or intravenous injection; the dosage varies with different geographical regions and expert advice should be obtained. Skin lesions can also be treated with sodium stibogluconate.**Amphotericin** is used with or after an antimony compound for visceral leishmaniasis unresponsive to the antimonial alone; side-effects may be reduced by using liposomal amphotericin (*AmBisome[®]*—section 5.2.3) at a dose of 1–3 mg/kg daily for 10–21 days to a cumulative dose of 21–30 mg/kg or at a dose of 3 mg/kg for 5 consecutive days followed by a single dose of 3 mg/kg 6 days later. *Abelcet[®]*, a lipid formulation of amphotericin is also likely to be effective but less information is available.**Pentamidine isetionate** (pentamidine isethionate) (section 5.4.8) has been used in antimony-resistant visceral leishmaniasis, but although the initial response is often good, the relapse rate is high; it is associated with serious side-effects. Other treatments include paromomycin [unlicensed], available from 'special-order' manufacturers or specialist importing companies, see p. 840**SODIUM STIBOGLUCONATE****Cautions** intravenous injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or substernal pain; mucocutaneous disease (see below); treat intercurrent infection (e.g. pneumonia); monitor ECG before and during treatment; heart disease (withdraw if conduction disturbances occur); predisposition to QT interval pro-

longation (including concomitant use with drugs that prolong the QT interval); **interactions:** Appendix 1 (sodium stibogluconate)

Mucocutaneous disease Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around the lesions (may be life-threatening if pharyngeal or tracheal involvement)—may require corticosteroid

Hepatic impairment use with caution

Renal impairment avoid in significant impairment

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding amount probably too small to be harmful

Side-effects anorexia, nausea, vomiting, abdominal pain; ECG changes; coughing (see Cautions); headache, lethargy, arthralgia, myalgia; *rarely* jaundice, flushing, bleeding from nose or gum, substernal pain (see Cautions), vertigo, fever, sweating, and rash; also reported pancreatitis and anaphylaxis; pain and thrombosis on intravenous administration, intramuscular injection also painful

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Leishmaniasis for dose, see notes above

Administration injection should be filtered immediately before administration using a filter of 5 microns or less; see also Cautions above

Pentostam® (GSK) 

Injection, sodium stibogluconate equivalent to pentavalent antimony 100 mg/mL. Net price 100-mL bottle = £66.43

5.4.6 Trypanocides

The prophylaxis and treatment of trypanosomiasis is difficult and differs according to the strain of organism. Expert advice should therefore be obtained.

5.4.7 Drugs for toxoplasmosis

Most infections caused by *Toxoplasma gondii* are self-limiting, and treatment is not necessary. Exceptions are children with eye involvement (toxoplasma chorooidoretinitis), and those who are immunosuppressed. Toxoplasmic encephalitis is a common complication of AIDS. The treatment of choice is a combination of pyrimethamine and sulfadiazine, given for several weeks (expert advice **essential**). Pyrimethamine is a folate antagonist, and adverse reactions to this combination are relatively common (folinic acid supplements (see p. 422) and weekly blood counts needed). Alternative regimens use combinations of pyrimethamine with clindamycin or clarithromycin or azithromycin. Long-term secondary prophylaxis is required after treatment of toxoplasmosis in immunocompromised patients; prophylaxis should continue until immunity recovers.

If toxoplasmosis is acquired in pregnancy, transplacental infection may lead to severe disease in the fetus; specialist advice should be sought on management. Spiramycin may reduce the risk of transmission of maternal infection to the fetus. When there is evidence of placental or fetal infection, pyrimethamine may be given with sulfadiazine and folinic acid after the first trimester.

In neonates without signs of toxoplasmosis, but born to mothers known to have become infected, spiramycin is given while awaiting laboratory results. If toxoplasmosis is confirmed in the infant, pyrimethamine and sulfadiazine are given for 12 months, together with folinic acid.

PYRIMETHAMINE

Cautions blood counts required with prolonged treatment; predisposition to folate deficiency; history of seizures—avoid large loading doses; **interactions:** Appendix 1 (pyrimethamine)

Hepatic impairment manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy theoretical teratogenic risk in first trimester (folate antagonist); adequate folate supplement should be given to mother

Breast-feeding present in milk—avoid breast-feeding during toxoplasmosis treatment; avoid other folate antagonists

Side-effects nausea, vomiting, diarrhoea, headache, dizziness, blood disorders with high doses (including anaemia, leucopenia, thrombocytopenia), rash; *less commonly* fever, abnormal skin pigmentation; *very rarely* colic, buccal ulceration, convulsions

Licensed use not licensed for use in children under 5 years

Indications and dose

Toxoplasmosis in pregnancy (in combination with sulfadiazine and folinic acid (section 8.1)), see notes above

- By mouth

Child 12–18 years 50 mg once daily until delivery

Congenital toxoplasmosis (in combination with sulfadiazine and folinic acid (section 8.1)),

- By mouth

Neonate 1 mg/kg twice daily for 2 days, *then* 1 mg/kg once daily for 6 months, *then* 1 mg/kg 3 times a week for 6 months

Malaria no dose stated because not recommended alone

Daraprim® (GSK) 

Tablets, scored, pyrimethamine 25 mg. Net price 30-tab pack = £13.00

SPIRAMYCIN

Cautions cardiac disease, arrhythmias (including pre-disposition to QT interval prolongation)

Contra-indications sensitivity to other macrolides

Hepatic impairment use with caution

Breast-feeding present in breast milk

Side-effects gastro-intestinal disturbances including nausea, vomiting, diarrhoea; dizziness, headache; rash; hepatotoxicity; *rarely*, prolongation of QT interval, thrombocytopenia and vasculitis

Licensed use not licensed

Indications and dose

Toxoplasmosis in pregnancy see notes above

- By mouth

Child 12–18 years 1.5 g twice daily until delivery

Chemoprophylaxis of congenital toxoplasmosis

- By mouth

Neonate 50 mg/kg twice daily

Spiramycin (Non-proprietary)

Tablets, spiramycin 750 000 units (250 mg); 1.5 million units (500 mg); 3 million units (1 g)

Syrup, spiramycin 75 000 units/mL (25 mg/mL)

Note 3000 units = 1 mg spiramycin

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

SULFADIAZINE

(Sulphadiazine)

Cautions see under Co-trimoxazole, section 5.1.8; interactions: Appendix 1 (sulfonamides)

Contra-indications see under Co-trimoxazole, section 5.1.8

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe impairment

Renal impairment use with caution in mild to moderate impairment; avoid in severe impairment; high risk of crystalluria

Pregnancy risk of neonatal haemolysis and methaemoglobinaemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded

Breast-feeding small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants

Side-effects see under Co-trimoxazole, section 5.1.8; also hypothyroidism, benign intracranial hypertension, optic neuropathy

Licensed use not licensed for use in toxoplasmosis

Indications and dose

Toxoplasmosis in pregnancy (in combination with pyrimethamine and folinic acid (section 8.1)), see notes above

- By mouth

Child 12–18 years 1 g 3 times daily until delivery

Congenital toxoplasmosis (in combination with pyrimethamine and folinic acid (section 8.1))

- By mouth

Neonate 50 mg/kg twice daily for 12 months

Sulfadiazine

(Non-proprietary) [PoM]

Tablets, sulfadiazine 500 mg, net price 56-tab pack = £57.15. Label: 9, 27

5.4.8 Drugs for pneumocystis pneumonia

Pneumonia caused by *Pneumocystis jirovecii* (*Pneumocystis carinii*) occurs in immunosuppressed children; it is a common cause of pneumonia in AIDS. Pneumocystis pneumonia should generally be treated by those experienced in its management. Blood gas measurement is used to assess disease severity.

Treatment

The recommended duration of treatment is generally 14–21 days.

Mild to moderate disease Co-trimoxazole (section 5.1.8) in high dosage is the drug of choice for the treatment of mild to moderate pneumocystis pneumonia.

Atovaquone or a combination of **dapsone** with **trimethoprim** 5 mg/kg every 6–8 hours (section 5.1.8) is given by mouth for the treatment of mild to moderate disease [unlicensed indication] in children who cannot tolerate co-trimoxazole.

A combination of **clindamycin** (section 5.1.6) and **primaquine** (section 5.4.1) may be used in the treatment of mild to moderate disease [unlicensed indication]; this combination is associated with considerable toxicity.

Severe disease Co-trimoxazole (section 5.1.8) in high dosage, given by mouth or by intravenous infusion, is the drug of choice for the treatment of severe pneumocystis pneumonia. **Pentamidine isetionate** given by intravenous infusion is an alternative for children who cannot tolerate co-trimoxazole, or who have not responded to it. Pentamidine isetionate is a potentially toxic drug that can cause severe hypotension during or immediately after infusion. If there is clinical improvement after 7–10 days of intravenous therapy with pentamidine isetionate, patients can be switched to oral treatment (e.g. atovaquone) to complete 21 days treatment.

Corticosteroid treatment can be lifesaving in those with severe pneumocystis pneumonia (see Adjunctive Therapy below).

Adjunctive therapy In moderate to severe pneumocystis infections associated with HIV infection, prednisolone (section 6.3.2) is given by mouth in a dose of 2 mg/kg (max. 80 mg daily) for 5 days (alternatively, hydrocortisone may be given parenterally); the dose is then reduced over the next 16 days and then stopped. Corticosteroid treatment should ideally be started at the same time as the anti-pneumocystis therapy and certainly no later than 24–72 hours afterwards. The corticosteroid should be withdrawn before anti-pneumocystis treatment is complete.

Prophylaxis

Prophylaxis against pneumocystis pneumonia should be given to all children with a history of this infection, and to all HIV-infected infants aged 1 month–1 year. Prophylaxis against pneumocystis pneumonia should also be considered for severely immunocompromised children. Prophylaxis should continue until immunity recovers sufficiently. It should not be discontinued if the child has oral candidiasis, continues to lose weight, or is receiving cytotoxic therapy or long-term immunosuppressant therapy.

Prophylaxis should also be given to infants aged 1 month–1 year who are suspected to be HIV-positive, or whose mothers had a viral load greater than 1000 HIV RNA copies/mL between 36 weeks' gestation and delivery; prophylaxis should be continued until HIV infection is excluded or until immunity recovers.

Co-trimoxazole (section 5.1.8) by mouth is the drug of choice for prophylaxis against pneumocystis pneumonia. Co-trimoxazole may be used in infants born to mothers with a high risk of transmission of infection.

Inhaled **pentamidine isetionate** is better tolerated than parenteral pentamidine. Intermittent inhalation of pentamidine isetionate is used for prophylaxis against pneumocystis pneumonia in children unable to tolerate co-trimoxazole. It is effective but children may be prone to extrapulmonary infection. Alternatively, **dapsone** can be used.

ATOVAQUONE

Cautions initial diarrhoea and difficulty in taking with food may reduce absorption (and require alternative therapy); other causes of pulmonary disease should

be sought and treated; **interactions:** Appendix 1 (atovaquone)

Hepatic impairment manufacturer advises caution—monitor more closely

Renal impairment manufacturer advises caution—monitor more closely

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid

Side-effects nausea, diarrhoea, vomiting, headache, insomnia, fever, anaemia, neutropenia, hyponatraemia, rash, pruritus; also reported, Stevens-Johnson syndrome

Licensed use not licensed for use in children

Indications and dose

Treatment of *Pneumocystis jirovecii* (*P. carinii*) pneumonia in children intolerant of co-trimoxazole

• By mouth

Child 1–3 months 15–20 mg/kg twice daily with food (particularly high fat) for 14–21 days

Child 3 months–2 years 22.5 mg/kg twice daily with food (particularly high fat) for 14–21 days

Child 2–18 years 15–20 mg/kg (max. 750 mg) twice daily with food (particularly high fat) for 14–21 days

Wellvone® (GSK) (PoM)

Suspension, sugar-free, atovaquone 750 mg/5 mL, net price 226 mL (tutti-frutti-flavoured) = £405.31. Label: 21

▲ With proguanil hydrochloride

See section 5.4.1

DAPSONE

Cautions cardiac or pulmonary disease; anaemia (treat severe anaemia before starting); susceptibility to haemolysis including G6PD deficiency (section 9.1.5); avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (dapsones)

Blood disorders On long-term treatment, children and their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop

Pregnancy neonatal haemolysis and methaemoglobinemia reported in third trimester; folic acid 5 mg daily should be given to mother throughout pregnancy

Breast-feeding haemolytic anaemia; although significant amount in milk, risk to infant very small unless infant is G6PD deficient

Side-effects haemolysis, methaemoglobinemia, neuropathy, allergic dermatitis (rarely including toxic epidermal necrolysis and Stevens-Johnson syndrome), anorexia, nausea, vomiting, tachycardia, headache, insomnia, psychosis, hepatitis, agranulocytosis; dapsones syndrome (rash with fever and eosinophilia)—discontinue immediately (may progress to exfoliative dermatitis, hepatitis, hyponatraemia, psychosis and death)

Licensed use not licensed for treatment of *P. jirovecii* pneumonia; monotherapy not licensed for children for prophylaxis of *P. jirovecii* pneumonia

Indications and dose

Treatment of *Pneumocystis jirovecii* (*P. carinii*) pneumonia (in combination with trimethoprim)

• By mouth

Child 1 month–12 years 2 mg/kg (max. 100 mg) once daily

Child 13–18 years 100 mg once daily

Prophylaxis of *Pneumocystis jirovecii* (*P. carinii*) pneumonia

• By mouth

Child 1 month–18 years 2 mg/kg (max. 100 mg) once daily

Dapsone (Non-proprietary) (PoM)

Tablets, dapsones 50 mg, net price 28-tab pack = £46.69; 100 mg 28-tab pack = £92.82. Label: 8

PENTAMIDINE ISETIONATE

Cautions risk of severe hypotension following administration (monitor blood pressure before starting treatment, during administration, and at regular intervals until treatment concluded; child should be lying down when receiving drug parenterally); hypokalaemia, hypomagnesaemia, coronary heart disease, bradycardia, history of ventricular arrhythmias, concomitant use with other drugs known to prolong Q-T interval; hypertension or hypotension; hyperglycaemia or hypoglycaemia; leucopenia, thrombocytopenia, or anaemia; carry out laboratory monitoring according to product literature; care required to protect personnel during handling and administration; **interactions:** Appendix 1 (pentamidine isetionate)

Hepatic impairment use with caution

Renal impairment reduce intravenous dose for pneumocystis pneumonia if creatinine clearance less than 10 mL/minute: in *life-threatening infection*, use 4 mg/kg once daily for 7–10 days, then 4 mg/kg on alternate days to complete course of at least 14 doses; in *less severe infection*, use 4 mg/kg on alternate days for at least 14 doses

Pregnancy manufacturer advises avoid unless essential

Breast-feeding manufacturer advises avoid unless essential—no information available

Side-effects severe reactions, sometimes fatal, due to hypotension, hypoglycaemia, pancreatitis, and arrhythmias; also leucopenia, thrombocytopenia, acute renal failure, hypocalcaemia; also reported: azotaemia, abnormal liver-function tests, anaemia, hyperkalaemia, nausea and vomiting, dizziness, syncope, flushing, hyperglycaemia, rash, and taste disturbances; Stevens-Johnson syndrome reported; on inhalation, bronchoconstriction (may be prevented by prior use of bronchodilators), cough and shortness of breath; discomfort, pain, induration, abscess formation, and muscle necrosis at injection site

Licensed use not licensed for prevention of pneumocystis pneumonia in children

Indications and dose

Treatment of *Pneumocystis jirovecii* (*P. carinii*) pneumonia

• By intravenous infusion

Child 1 month–18 years 4 mg/kg once daily

Prophylaxis of *Pneumocystis jirovecii* (*P. carinii*) pneumonia

- By inhalation of nebulised solution (using suitable equipment—consult product literature)
Child 5–18 years 300 mg every 4 weeks or 150 mg every 2 weeks

Visceral leishmaniasis (kala-azar, section 5.4.5)

- By deep intramuscular injection
Child 1–18 years 3–4 mg/kg on alternate days to max. total of 10 injections; course may be repeated if necessary

Cutaneous leishmaniasis

- By deep intramuscular injection
Child 1–18 years 3–4 mg/kg once or twice weekly until condition resolves (but see also section 5.4.5)

Trypanosomiasis

- By deep intramuscular injection or intravenous infusion
Child 1–18 years 4 mg/kg daily or on alternate days to total of 7–10 injections

Administration Direct intravenous injection should be avoided whenever possible and **never** given rapidly; intramuscular injections should be deep and preferably given into the buttock.

For intravenous infusion, reconstitute 300 mg with 3–5 mL Water for Injections (displacement value may be significant), then dilute required dose with 50–250 mL Glucose 5% or Sodium Chloride 0.9%; give over at least 60 minutes

Pentacarinat® (Sanofi-Aventis) (PoM)

Injection, powder for reconstitution, pentamidine isetonate, net price 300-mg vial = £31.77

Caution in handling Pentamidine isetonate is toxic and personnel should be adequately protected during handling and administration—consult product literature

Note Pentacarinat® Injection (dissolved in water for injection) may be used for nebulisation

5.5 Anthelmintics

- 5.5.1 **Drugs for threadworms**
- 5.5.2 **Ascaricides**
- 5.5.3 **Drugs for tapeworm infections**
- 5.5.4 **Drugs for hookworms**
- 5.5.5 **Schistosomicides**
- 5.5.6 **Filaricides**
- 5.5.7 **Drugs for cutaneous larva migrans**
- 5.5.8 **Drugs for strongyloidiasis**

Advice on prophylaxis and treatment of helminth infections is available from the following specialist centres:

Birmingham	(0121) 424 0357
Scottish Centre for Infection and Environmental Health (registered users of Travax only)	(0141) 300 1100 (weekdays 12–5 p.m. only)
Liverpool	(0151) 705 3100
London	(0845) 155 5000 (treatment)

5.5.1 Drugs for threadworms (pinworms, *Enterobius vermicularis*)

Anthelmintics are effective in threadworm infections, but their use needs to be combined with hygienic measures to break the cycle of auto-infection. All members of the family require treatment.

Adult threadworms do not live for longer than 6 weeks and for development of fresh worms, ova must be swallowed and exposed to the action of digestive juices in the upper intestinal tract. Direct multiplication of worms does not take place in the large bowel. Adult female worms lay ova on the perianal skin which causes pruritus; scratching the area then leads to ova being transmitted on fingers to the mouth, often via food eaten with unwashed hands. Washing hands and scrubbing nails before each meal and after each visit to the toilet is essential. A bath taken immediately after rising will remove ova laid during the night.

Mebendazole is the drug of choice for treating threadworm infection in children over 6 months. It is given as a single dose; as reinfection is very common, a second dose may be given after 2 weeks.

MEBENDAZOLE

Cautions interactions: Appendix 1 (mebendazole)

Note The patient information leaflet in the *Vermox*® pack includes the statement that it is not suitable for women known to be pregnant or for children under 2 years

Pregnancy manufacturer advises avoid—toxicity in animal studies

Breast-feeding amount present in milk too small to be harmful but manufacturer advises avoid

Side-effects abdominal pain; *less commonly* diarrhoea, flatulence; *rarely* hepatitis, convulsions, dizziness, neutropenia, urticaria, alopecia, rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis)

Licensed use not licensed for use in children under 2 years

Indications and dose**Threadworms**

- By mouth
Child 6 months–18 years 100 mg as a single dose; if reinfection occurs second dose may be needed after 2 weeks

Whipworms, hookworms (section 5.5.4)

- By mouth
Child 1–18 years 100 mg twice daily for 3 days

Roundworms (section 5.5.2)

- By mouth
Child 1–2 years 100 mg twice daily for 3 days
Child 2–18 years 100 mg twice daily for 3 days or 500 mg as a single dose

1 Mebendazole (Non-proprietary) (PoM)

Tablets, chewable, mebendazole 100 mg

- Mebendazole tablets can be sold to the public if supplied for oral use in the treatment of enterobiasis in children over 2 years provided its container or package is labelled to show a max. single dose of 100 mg and it is supplied in a container or package containing not more than 800 mg

Vermox® (Janssen) (PoM)

Tablets, orange, scored, chewable, mebendazole 100 mg. Net price 6-tab pack = £1.36

Oral suspension, mebendazole 100 mg/5 mL (banana-flavoured). Net price 30 mL = £1.59

5.5.2 Ascaricides (common roundworm infections)

Mebendazole (section 5.5.1) is effective against *Ascaris lumbricoides* and is generally considered to be the drug of choice.

Levamisole [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 840) is an alternative when mebendazole cannot be used. It is very well tolerated; mild nausea or vomiting has been reported in about 1% of treated patients.

LEVAMISOLE

Cautions epilepsy; juvenile idiopathic arthritis; Sjögren's syndrome

Contra-indications blood disorders

Hepatic impairment use with caution—dose adjustment may be necessary

Pregnancy embryotoxic in *animal* studies, avoid if possible

Breast-feeding no information available

Side-effects nausea, vomiting, diarrhoea; dizziness, headache; on *prolonged treatment* taste disturbances, insomnia, convulsions, influenza-like syndrome, blood disorders, vasculitis, arthralgia, myalgia, rash

Licensed use not licensed

Indications and dose

Roundworm (*Ascaris lumbricoides*)

- By mouth

Child 1 month–18 years 2.5–3 mg/kg (max. 150 mg) as a single dose

Hookworm

- By mouth

Child 1 month–18 years 2.5 mg/kg (max. 150 mg) as a single dose repeated after 7 days if severe

Nephrotic syndrome (specialist supervision section 6.3.2)

- By mouth

Child 1 month–18 years 2.5 mg/kg (max. 150 mg) on alternate days

Levamisole (Non-proprietary) (PoM)

Tablets, levamisole (as hydrochloride) 50 mg. Label: 4

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

5.5.3 Drugs for tapeworm infections

Taenicides

Niclosamide [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 840) is the most widely used drug for tapeworm infections and side-effects are limited to occasional gastro-intestinal upset, lightheadedness, and pruritus;

it is not effective against larval worms. Fears of developing cysticercosis in *Taenia solium* infections have proved unfounded. All the same, an antiemetic can be given before treatment and a laxative can be given 2 hours after niclosamide.

Praziquantel [unlicensed] is available from Merck Serono (*Cysticide*®); it is as effective as niclosamide and is given to children over 4 years of age as a single dose of 5–10 mg/kg after a light breakfast (or as a single dose of 25 mg/kg for *Hymenolepis nana*).

Hydatid disease

Cysts caused by *Echinococcus granulosus* grow slowly and asymptomatic children do not always require treatment. Surgical treatment remains the method of choice in many situations. **Albendazole** [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 840) is used in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases. Albendazole is given to children over 2 years of age in a dose of 7.5 mg/kg twice daily (max. 400 mg twice daily) for 28 days followed by 14-day break and then repeated for up to 2–3 cycles. Alveolar echinococcosis due to *E. multilocularis* is usually fatal if untreated. Surgical removal with albendazole cover is the treatment of choice, but where effective surgery is impossible, repeated cycles of albendazole (for a year or more) may help. Careful monitoring of liver function is particularly important during drug treatment.

5.5.4 Drugs for hookworms (ancylostomiasis, necatoriasis)

Hookworms live in the upper small intestine and draw blood from the point of their attachment to their host. An iron-deficiency anaemia may occur and, if present, effective treatment of the infection requires not only expulsion of the worms but treatment of the anaemia.

Mebendazole (section 5.5.1) has a useful broad-spectrum activity, and is effective against hookworms. **Albendazole** [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 840) given as a single dose of 400 mg in children over 2 years, is an alternative. **Levamisole** is also effective (section 5.5.2).

5.5.5 Schistosomicides (bilharziasis)

Adult *Schistosoma haematobium* worms live in the genital-urinary veins and adult *S. mansoni* in those of the colon and mesentery. *S. japonicum* is more widely distributed in veins of the alimentary tract and portal system.

Praziquantel [unlicensed] is available from Merck Serono (*Cysticide*®) and is effective against all human schistosomes. In children over 4 years the dose is 20 mg/kg followed after 4–6 hours by a further dose of 20 mg/kg (20 mg/kg 3 times daily for one day for *S. japonicum* infections). No serious adverse effects have been reported. Of all the available schistosomicides, it has the most attractive combination of effectiveness, broad-spectrum activity, and low toxicity.

5.5.6 Filaricides

Diethylcarbamazine [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 840) is effective against microfilariae and adult worms of *Loa loa*, *Wuchereria bancrofti*, and *Brugia malayi*. To minimise reactions, treatment in children over 1 month is commenced with a dose of diethylcarbamazine citrate 1 mg/kg in divided doses on the first day and increased gradually over 3 days to 6 mg/kg daily (3 mg/kg daily if child under 10 years) in divided doses; length of treatment varies according to infection type, and usually gives a radical cure for these infections. Close medical supervision is necessary particularly in the early phase of treatment. In heavy infections there may be a febrile reaction, and in heavy *Loa loa* infection there is a small risk of encephalopathy. In such cases specialist advice should be sought, and treatment must be given under careful in-patient supervision and stopped at the first sign of cerebral involvement.

Ivermectin [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 840) is very effective in *onchocerciasis* and it is now the drug of choice. In children over 5 years, a single dose of 150 micrograms/kg by mouth produces a prolonged reduction in microfilarial levels. Retreatment at intervals of 6 to 12 months depending on symptoms must be given until the adult worms die out. Reactions are usually slight and most commonly take the form of temporary aggravation of itching and rash. Diethylcarbamazine or suramin should no longer be used for *onchocerciasis* because of their toxicity.

5.5.7 Drugs for cutaneous larva migrans (creeping eruption)

Dog and cat hookworm larvae may enter human skin where they produce slowly extending itching tracks usually on the foot. Single tracks can be treated with topical tiabendazole (no commercial preparation available). Multiple infections respond to **ivermectin**, **albendazole** or **tiabendazole** (thiabendazole) by mouth (all unlicensed and available from 'special-order' manufacturers or specialist importing companies, see p. 840).

5.5.8 Drugs for strongyloidiasis

Adult forms of *Strongyloides stercoralis* live in the gut and produce larvae which penetrate the gut wall and invade the tissues, setting up a cycle of auto-infection. **Ivermectin** [unlicensed] in a dose of 200 micrograms/kg daily for 2 days is the treatment of choice for chronic *Strongyloides* infection in children over 5 years. **Albendazole** [unlicensed] is an alternative in children over 2 years given in a dose of 400 mg twice daily for 3 days, repeated after 3 weeks if necessary.

Both of these drugs are available from 'special-order' manufacturers or specialist importing companies, see p. 840.

6 Endocrine system

6.1 Drugs used in diabetes	355
6.1.1 Insulins	356
6.1.1.1 Short-acting insulins	359
6.1.1.2 Intermediate- and long-acting insulins	360
6.1.1.3 Hypodermic equipment	363
6.1.2 Antidiabetic drugs	364
6.1.2.1 Sulfonylureas	364
6.1.2.2 Biguanides	366
6.1.2.3 Other antidiabetic drugs	366
6.1.3 Diabetic ketoacidosis	366
6.1.4 Treatment of hypoglycaemia	367
6.1.5 Treatment of diabetic nephropathy and neuropathy	369
6.1.6 Diagnostic and monitoring devices for diabetes mellitus	369
6.2 Thyroid and antithyroid drugs	372
6.2.1 Thyroid hormones	372
6.2.2 Antithyroid drugs	373
6.3 Corticosteroids	375
6.3.1 Replacement therapy	375
6.3.2 Glucocorticoid therapy	376
6.4 Sex hormones	383
6.4.1 Female sex hormones	383
6.4.1.1 Oestrogens	383
6.4.1.2 Progestogens	384
6.4.2 Male sex hormones and antagonists	384
6.4.3 Anabolic steroids	387
6.5 Hypothalamic and pituitary hormones	387
6.5.1 Hypothalamic and anterior pituitary hormones including growth hormone	387
6.5.2 Posterior pituitary hormones and antagonists	390
6.6 Drugs affecting bone metabolism	393
6.6.1 Calcitonin	393
6.6.2 Bisphosphonates	394
6.7 Other endocrine drugs	396
6.7.1 Bromocriptine and other dopaminergic drugs	396
6.7.2 Drugs affecting gonadotrophins	396
6.7.3 Metyrapone	396
6.7.4 Somatomedins	397

This chapter includes advice on the drug management of the following:

Adrenal suppression during illness, trauma or surgery, p. 377
 Serious infections in patients taking corticosteroids, p. 377
 Nephrotic syndrome, p. 377
 Delayed puberty, p. 383
 Precocious puberty, p. 385
 Diabetes insipidus, p. 390

For hormonal contraception, see section 7.3.

6.1 Drugs used in diabetes

6.1.1 Insulins
6.1.2 Antidiabetic drugs
6.1.3 Diabetic ketoacidosis
6.1.4 Treatment of hypoglycaemia
6.1.5 Treatment of diabetic nephropathy and neuropathy
6.1.6 Diagnostic and monitoring devices for diabetes mellitus

Diabetes mellitus occurs because of a lack of insulin or resistance to its action. It is diagnosed by measuring fasting or random blood-glucose concentration (and occasionally by oral glucose tolerance test). Although there are many subtypes, the two principle classes of diabetes are type 1 diabetes and type 2 diabetes.

Type 1 diabetes, (formerly referred to as insulin-dependent diabetes mellitus (IDDM)), is due to a deficiency of insulin following autoimmune destruction of pancreatic beta cells and is the most common form of diabetes in children. Children with type 1 diabetes require administration of insulin.

Type 2 diabetes, (formerly referred to as non-insulin-dependent diabetes mellitus (NIDDM)), is rare in children but the incidence is increasing, particularly in adolescents, as obesity increases. It results from reduced secretion of insulin or from peripheral resistance to the action of insulin, or from a combination of both. Although children may be controlled on diet alone, many require oral antidiabetic drugs or insulin to maintain satisfactory control. There is limited information available on the use of oral anti-diabetic drugs in children (see section 6.1.2). In overweight individuals, type 2 diabetes may be prevented by losing weight and increasing physical activity.

Genetic defects of beta-cell function (formerly referred to as maturity-onset diabetes of the young (MODY)), describes a number of rare disease states, characterised by onset of mild hyperglycaemia, generally before 25 years of age. A sulfonylurea, such as gliclazide (p. 365), may be effective in these patients.

Treatment of diabetes Treatment should be aimed at alleviating symptoms and minimising the risk of long-term complications (see below).

Diabetes is a strong risk factor for cardiovascular disease later in life. Other risk factors for cardiovascular disease (smoking, hypertension, obesity and hyperlipidaemia) should be addressed. The use of an ACE inhibitor (section 2.5.5.1) and of a lipid-regulating drug (section 2.12) can be beneficial in children with diabetes and a high cardiovascular disease risk. For reference to the use of an ACE inhibitor in the management of diabetic nephropathy, see section 6.1.5.

Prevention of diabetic complications Although rare, retinopathy, neuropathy and nephropathy can occur in children with diabetes. Screening for complications should begin 5 years after diagnosis of diabetes or from 12 years of age. Optimal glycaemic control in both type 1 diabetes and type 2 diabetes reduces, in the long term, the risk of microvascular complications including retinopathy, development of proteinuria and to some extent neuropathy.

A measure of the total glycosylated (or glycated) haemoglobin (HbA_{1c}) or a specific fraction (HbA_{1c}) provides a good indication of long-term glycaemic control. Overall it is ideal to aim for an HbA_{1c} concentration of 48–59 mmol/mol or less (reference range 20–42 mmol/mol), but this cannot always be achieved and for those using insulin there is a significantly increased risk of disabling hypoglycaemia.

Measurement of HbA_{1c}

HbA_{1c} values are expressed in mmol of glycosylated haemoglobin per mol of haemoglobin (mmol/mol), a standardised unit specific for HbA_{1c} created by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). HbA_{1c} values were previously aligned to the assay used in the Diabetes Control and Complications Trial (DCC^T) and expressed as a percentage.

Equivalent values

IFCC- HbA_{1c} (mmol/mol)	DCC ^T - HbA_{1c} (%)
42	6.0
48	6.5
53	7.0
59	7.5
64	8.0
75	9.0

Laboratory measurement of serum-fructosamine concentration is technically simpler and cheaper than the measurement of HbA_{1c} and can be used to assess control over short periods of time, particularly when HbA_{1c} monitoring is invalid (e.g. disturbed erythrocyte turnover or abnormal haemoglobin type).

Tight control of blood pressure in hypertensive children with type 2 diabetes may reduce mortality significantly and protects visual acuity (by reducing considerably the risks of maculopathy and retinal photocoagulation) (see also section 2.5).

Driving Information on the requirements for driving vehicles by individuals receiving treatment for diabetes is available in the BNF (section 6.1) or from the DVLA at www.gov.uk/government/publications/at-a-glance.

6.1.1 Insulins

6.1.1.1 Short-acting insulins

6.1.1.2 Intermediate- and long-acting insulins

6.1.1.3 Hypodermic equipment

Insulin is a polypeptide hormone that plays a key role in the regulation of carbohydrate, fat, and protein metabolism. There are differences in the amino-acid sequence of animal insulins, human insulins, and the human insulin analogues. Human sequence insulin may be produced semisynthetically by enzymatic modification of porcine insulin (emp) or biosynthetically by recombinant DNA technology using bacteria (crb, prb) or yeast (pyr).

Immunological resistance to insulin action is uncommon. Preparations of human sequence insulin should theoretically be less immunogenic than other insulin preparations, but no real advantage has been shown in trials.

Insulin is inactivated by gastro-intestinal enzymes, and must therefore be given by injection; the subcutaneous route is ideal in most circumstances. Insulin is usually injected into the thighs, buttocks, or abdomen; absorption from a limb site can be increased if the limb is used in strenuous exercise after the injection. Generally, subcutaneous insulin injections cause few problems; lipodystrophy may occur and is a factor in poor glycaemic control. Lipodystrophy can be minimised by using different injection sites in rotation. Local allergic reactions are rare.

Insulin should be given to all children with type 1 diabetes; it may also be needed to treat type 2 diabetes either when other methods cannot control the condition or during periods of acute illness or peri-operatively. Insulin is required in all instances of ketoacidosis (section 6.1.3), which can develop rapidly in children.

NHS Diabetes guidance

Safe and Effective Use of Insulin in Hospitalised Patients (March 2010)

Available at www.diabetes.nhs.uk

Management of diabetes with insulin The aim of treatment is to achieve the best possible control of blood-glucose concentration without making the child or carer obsessional and to avoid disabling hypoglycaemia; close co-operation is needed between the child or carer and the medical team to achieve good control and thereby reduce the risk of complications.

Insulin preparations can be divided into 3 types:

- those of **short** duration which have a relatively rapid onset of action, namely soluble insulin and the rapid-acting insulin analogues, insulin aspart, insulin glulisine, and insulin lispro (section 6.1.1.1);
- those with an **intermediate** action, e.g. isophane insulin (section 6.1.1.2); and
- those whose action is slower in onset and lasts for **long** periods, e.g. protamine zinc insulin, insulin detemir, and insulin glargine (section 6.1.1.2).

The duration of action of a particular type of insulin can vary from one child to another, and needs to be assessed individually.

Mixtures of insulin preparations may be required and appropriate combinations have to be determined for the individual child. Treatment should be started with several doses of short-acting insulin (soluble insulin or a rapid-acting insulin analogue) given throughout the day with a longer-acting insulin given once or twice daily. Alternatively, for those who have difficulty with, or prefer not to use, multiple daily injection regimens or in whom such regimens fail to achieve adequate glycaemic control, a mixture of premixed short- and intermediate-acting insulins (most commonly in a proportion of 30% soluble insulin and 70% isophane insulin) can be given twice daily. The dose of short-acting or rapid-acting insulin (or the proportion of the short-acting soluble insulin component in premixed insulin) can be increased in those with excessive postprandial hyperglycaemia. The dose of insulin is increased gradually according to the child's individual requirements, taking care to avoid troublesome hypoglycaemia.

Initiation of insulin may be followed by a partial remission phase or 'honeymoon period' when lower doses of insulin are required than are subsequently necessary to maintain glycaemic control.

Examples of insulin regimens

- Multiple injection regimen: short-acting insulin or rapid-acting insulin analogue, before meals
With intermediate-acting or long-acting insulin, once or twice daily;
- Short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin, twice daily (before breakfast and the main evening meal);
- Short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting insulin, before breakfast
With short-acting or rapid-acting insulin analogue alone, before afternoon snack or the main evening meal, and intermediate-acting insulin or long-acting insulin, at bedtime;
- Continuous subcutaneous insulin infusion (see below).

Insulin requirements Most prepubertal children require around 0.6–0.8 units/kg/day of insulin after the initial temporary remission phase. Unless the child has a very sedentary life-style, a requirement for higher doses may indicate poor compliance, poor absorption of insulin from the injection site (e.g. because of lipohypertrophic sites), or the beginning of puberty. During puberty up to 1.5–2 units/kg/day of insulin may be required, especially during growth spurts. Around 1 year after menarche or after the growth spurt in boys, the dose may need to be adjusted to avoid excessive weight gain. Insulin requirements can be *increased* by infection, stress, and accidental or surgical trauma. Insulin requirements can be *reduced* in very active individuals, in those with certain endocrine disorders (e.g. Addison's disease, hypopituitarism), or in coeliac disease. Insulin requirements should be assessed frequently in all these circumstances.

Hepatic impairment Insulin requirements may be decreased in patients with hepatic impairment.

Renal impairment Insulin requirements may decrease in patients with renal impairment and therefore dose reduction may be necessary. The compensatory response to hypoglycaemia is impaired in renal impairment.

Pregnancy and breast-feeding During pregnancy and breast-feeding, insulin requirements may alter and doses should be assessed frequently by an experienced diabetes physician. The dose of insulin generally needs to be increased in the second and third trimesters of pregnancy. The short-acting insulin analogues, insulin aspart and insulin lispro, are not known to be harmful, and may be used during pregnancy and breast-feeding. Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin is recommended where longer-acting insulins are needed; insulin detemir may also be considered.

Insulin administration Insulin is generally given by *subcutaneous injection*; the injection site should be rotated to prevent lipodystrophy. Injection devices ('pens') (section 6.1.1.3), which hold the insulin in a cartridge and meter the required dose, are convenient to use. Insulin syringes (for use with needles) are less popular with children and carers, but may be required for insulins not available in cartridge form.

For intensive insulin regimens multiple subcutaneous injections (3 or more times daily) are usually recommended.

Short-acting insulins (soluble insulin, insulin aspart, insulin glulisine, and insulin lispro) can also be given by *continuous subcutaneous infusion* using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for children who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens (see also NICE guidance below). Children on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration or have it monitored by a carer, and have expert training, advice, and supervision from an experienced healthcare team.

NICE guidance

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008)

Continuous subcutaneous insulin infusion is recommended as an option in children over 12 years with type 1 diabetes:

- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or
- whose glycaemic control remains inadequate (HbA_{1c} over 8.5% [69 mmol/mol]) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.

www.nice.org.uk/TA151

Soluble insulin by the *intravenous route* is reserved for urgent treatment e.g. in diabetic ketoacidosis, and for fine control in serious illness and in the peri-operative period (see under Diabetes and Surgery, below).

Monitoring All carers and children need to be trained to monitor blood-glucose concentrations (section 6.1.6). Since blood-glucose concentration varies substantially throughout the day, 'normoglycaemia' cannot always be achieved throughout a 24-hour period without causing damaging hypoglycaemia. It is therefore best to recommend that children should maintain a blood-glucose concentration of between 4 and 10 mmol/litre for most of the time (4–8 mmol/litre before meals and less than 10 mmol/litre after meals), while accepting that on occasions, for brief periods, it will be above these values; efforts should be made to prevent the blood-glucose concentration from falling below 4 mmol/litre. Children using multiple injection regimens should understand how to adjust their insulin dose according to their carbohydrate intake. With fixed-dose insulin regimens, the carbohydrate intake needs to be regulated, and should be distributed throughout the day to match the insulin regimen. The intake of energy and of simple and complex carbohydrates should be adequate to allow normal growth and development but obesity must be avoided.

Hypoglycaemia Hypoglycaemia is a potential problem for all children using insulin, and they and their carers should be given careful instruction on how to avoid it.

Very tight control of diabetes lowers the blood-glucose concentration needed to trigger hypoglycaemic symptoms; an increase in the frequency of hypoglycaemic episodes may reduce the warning symptoms experienced by the child. Loss of warning of hypoglycaemia among insulin-treated children can be a serious hazard, especially for cyclists and drivers.

To restore the warning signs, episodes of hypoglycaemia must be minimised; this involves appropriate adjustment of insulin type, dose, and frequency, together with suitable timing and quantity of meals and snacks.

Diabetes and surgery Children with type 1 diabetes should undergo surgery in centres with facilities for, and expertise in, the care of children with diabetes. Detailed local protocols should be available to all healthcare professionals involved in the treatment of these children.

Children with type 1 diabetes who require surgery:

- should be admitted to hospital for general anaesthesia;
- should receive insulin, even if they are fasting, to avoid ketoacidosis;
- should receive glucose infusion when fasting before an anaesthetic to prevent hypoglycaemia;
- should have careful monitoring of blood-glucose concentration because surgery may cause hyperglycaemia.

Elective surgery Surgery in children with diabetes is best scheduled early on the list, preferably in the morning. If glycaemic control is poor it is advisable to admit the child well in advance of surgery. On the evening before surgery, blood-glucose should be measured frequently, especially before meals and snacks and at bedtime; urine should be tested for ketones. The usual evening or bedtime insulin and bedtime snack should be given. Ketosis or severe hypoglycaemia require correction, preferably by overnight intravenous infusion (section 6.1.3 and

section 6.1.4), and the surgery may need to be postponed.

For *minor procedures that require fasting*, a slight modification of the usual regimen may be all that is necessary e.g. for early morning procedures delay insulin and food until immediately after the procedure.

For *other types of elective surgery*, consult local treatment protocols.

Emergency surgery Intravenous fluids and an insulin infusion should be started immediately (see Intravenous Fluids and Continuous Insulin Infusion, below). If ketoacidosis is present the recommendations for diabetic ketoacidosis should be followed (section 6.1.3).

Intravenous fluids and continuous insulin infusion Blood-glucose and plasma-electrolyte concentrations must be measured frequently in a child receiving intravenous support. Intravenous infusion should be continued until after the child starts to eat and drink. The following infusions should be used and adjusted according to the child's fluid and electrolyte requirements:

- Constant infusion of sodium chloride 0.45% and glucose 5% intravenous infusion together with potassium chloride 20 mmol/litre (provided that plasma-potassium concentration is not raised) at a rate determined by factors such as volume depletion and age; the amount of potassium chloride infused is adjusted according to plasma electrolyte measurements;
- Constant infusion of soluble insulin 1 unit/mL in sodium chloride 0.9% intravenous infusion initially at a rate of 0.025 units/kg/hour (up to 0.05 units/kg/hour if the child is unwell), then adjusted according to blood-glucose concentration (frequent monitoring necessary) in line with locally agreed protocols and the child's volume depletion and age;
- Blood-glucose concentration should be maintained between 5 and 10 mmol/litre. If the glucose concentration falls below 5 mmol/litre, glucose 10% intravenous infusion may be required; conversely, if the glucose concentration persistently exceeds 14 mmol/litre, sodium chloride 0.9% intravenous infusion should be substituted;
- The insulin infusion may be stopped temporarily for 10–15 minutes if blood-glucose concentration falls below 4 mmol/litre.

The usual subcutaneous insulin regimen should be started before the first meal (but the dose may need to be 10–20% higher than usual if the child is still bed-bound or unwell) and the intravenous insulin infusion stopped 1 hour later. If glycaemic control is not adequately achieved, additional insulin can be given in the following ways:

- additional doses of soluble insulin at any of the 4 injection times (before meals or bedtime) *or*
- temporary addition of intravenous insulin infusion to subcutaneous regimen *or*
- complete reversion to intravenous insulin infusion (particularly if the child is unwell).

Neonatal hyperglycaemia Newborn babies are relatively intolerant of glucose, especially in the first week of life and if premature. If intravenous glucose is necessary e.g. for total parenteral nutrition, infuse at a lower rate for 6–12 hours and the glucose intolerance

should resolve. Insulin is not needed for such transient glucose intolerance, but may be needed if blood-glucose concentration is persistently high.

Neonatal diabetes Neonatal diabetes is a rare condition that presents with acidosis, dehydration, hyperglycaemia, and rarely ketosis; it responds to continuous insulin infusion. When the neonate is stable, treatment can be switched to subcutaneous insulin given once or twice a day. Treatment is normally required for 4–6 weeks in transient forms, but may be required permanently in some cases.

6.1.1.1 Short-acting insulins

Soluble insulin is a short-acting form of insulin. For maintenance regimens it is usual to inject it 15 to 30 minutes before meals.

Soluble insulin is the most appropriate form of insulin for use in diabetic emergencies and at the time of surgery. It can be given intravenously and intramuscularly, as well as subcutaneously.

When injected subcutaneously, soluble insulin has a rapid onset of action (30 to 60 minutes), a peak action between 2 and 4 hours, and a duration of action of up to 8 hours.

When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes and its effect disappears within 30 minutes.

The rapid-acting human insulin analogues, **insulin aspart**, **insulin glulisine**, and **insulin lispro**, have a faster onset (10–20 minutes) and shorter duration of action (2–5 hours) than soluble insulin; as a result, compared with soluble insulin, fasting and preprandial blood-glucose concentrations are a little higher, postprandial blood-glucose concentration is a little lower, and hypoglycaemia occurs slightly less frequently. These rapid-acting insulins are ideal for prandial dosing in a multiple injection regimen in combination with a long-acting insulin once or twice daily. Insulin aspart, insulin glulisine, and insulin lispro can be administered by subcutaneous infusion (see Insulin Administration, above). Insulin aspart and insulin lispro can also be administered intravenously and can be used as alternatives to soluble insulin for diabetic emergencies and at the time of surgery.

INSULIN

(Insulin Injection; Neutral Insulin; Soluble Insulin)

A sterile solution of insulin (i.e. bovine or porcine) or of human insulin; pH 6.6–8.0

Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)

Hepatic impairment section 6.1.1

Renal impairment section 6.1.1

Pregnancy section 6.1.1

Breast-feeding section 6.1.1

Side-effects see notes above; transient oedema; local reactions and fat hypertrophy at injection site; rarely hypersensitivity reactions including urticaria, rash; overdose causes hypoglycaemia

Indications and dose

Hyperglycaemia during illness, neonatal diabetes, neonatal hyperglycaemia

• By intravenous infusion

Neonate 0.02–0.125 units/kg/hour, adjusted according to blood-glucose concentration, see also notes above

Child 1 month–18 years 0.025–0.1 units/kg/hour, adjusted according to blood-glucose concentration, see also notes above

Diabetes mellitus

• By subcutaneous injection

According to requirements (see notes above)

Note Rotate injection site to reduce local reactions and fat hypertrophy

Diabetic ketoacidosis section 6.1.3

Surgery in children with diabetes section 6.1.1

Administration For *intravenous infusion*, dilute to a concentration of 1 unit/mL with Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

Neonatal intensive care, dilute 5 units to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/kg/hour provides a dose of 0.01 units/kg/hour

Highly purified animal

Counselling Show container to child or carer and confirm the expected version is dispensed

Hypurin® Bovine Neutral (Wockhardt) (PoM)

Injection, soluble insulin (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £27.72; cartridges (for *Autopen® Classic*) 5 × 3 mL = £41.58

Hypurin® Porcine Neutral (Wockhardt) (PoM)

Injection, soluble insulin (porcine, highly purified) 100 units/mL. Net price 10-mL vial = £25.20; cartridges (for *Autopen® Classic*) 5 × 3 mL = £37.80

Human sequence

Counselling Show container to child or carer and confirm the expected version is dispensed

Actrapid® (Novo Nordisk) (PoM)

Injection, soluble insulin (human, pyr) 100 units/mL. Net price 10-mL vial = £7.48

Note Not recommended for use in subcutaneous insulin infusion pumps—may precipitate in catheter or needle

Humulin S® (Lilly) (PoM)

Injection, soluble insulin (human, prb) 100 units/mL. Net price 10-mL vial = £15.68; 5 × 3-mL cartridge (for *Autopen® Classic* or *HumaPen®*) = £19.08

Insuman® Rapid (Sanofi-Aventis) (PoM)

Injection, soluble insulin (human, crb) 100 units/mL, net price 5 × 3-mL cartridge (for *ClickSTAR®* and *Autopen® 24*) = £17.50

Note Not recommended for use in subcutaneous insulin infusion pumps

Mixed preparations

See Biphasic Isophane Insulin (section 6.1.1.2)

INSULIN ASPART

(Recombinant human insulin analogue)

Cautions section 6.1.1; interactions: Appendix 1 (antidiabetics)**Hepatic impairment** section 6.1.1**Renal impairment** section 6.1.1**Pregnancy** section 6.1.1**Breast-feeding** section 6.1.1**Side-effects** see under Insulin**Licensed use** not licensed for use in children under 2 years**Indications and dose****Diabetes mellitus**

- By subcutaneous injection
Immediately before meals or when necessary shortly after meals, according to requirements
- By subcutaneous infusion, or intravenous injection, or intravenous infusion
According to requirements

Administration for intravenous infusion, dilute to a concentration of 0.05–1 unit/mL with Glucose 5% or Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

NovoRapid® (Novo Nordisk) [PoM]

Injection, insulin aspart (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £14.08; *Penfill*® cartridge (for *Innovo*® and *Novo-Pen*® devices) 5 × 3-mL = £28.31; 5 × 3-mL *Flex-Pen*® prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.60; 5 × 3-mL *FlexTouch*® prefilled disposable injection devices (range 1–80 units, allowing 1-unit dosage adjustment) = £32.13

Counselling Show container to child or carer and confirm the expected version is dispensed

INSULIN GLULISINE

(Recombinant human insulin analogue)

Cautions section 6.1.1; interactions: Appendix 1 (antidiabetics)**Hepatic impairment** section 6.1.1**Renal impairment** section 6.1.1**Pregnancy** section 6.1.1**Breast-feeding** section 6.1.1**Side-effects** see under Insulin**Licensed use** not licensed for children under 6 years**Indications and dose****Diabetes mellitus**

- By subcutaneous injection
Immediately before meals or when necessary shortly after meals, according to requirements
- By subcutaneous infusion or intravenous infusion
According to requirements

Apidra® (Sanofi-Aventis) [PoM]

Injection, insulin glulisine (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £16.00; 5 × 3-mL cartridge (for *ClickSTAR*® and *Autopen*® 24) = £28.30; 5 × 3-mL *Apidra*® *SoloStar*® prefilled disposable injection devices (range 1–

80 units, allowing 1-unit dosage adjustment) = £28.30

Counselling Show container to patient and confirm that patient is expecting the version dispensed

Note The *Scottish Medicines Consortium* (p. 3) has advised (October 2008) that *Apidra*® is accepted for restricted use within NHS Scotland for the treatment of children over 6 years with diabetes mellitus in whom the use of a short-acting insulin analogue is appropriate

INSULIN LISPRO

(Recombinant human insulin analogue)

Cautions section 6.1.1; children under 12 years (use only if benefit likely compared to soluble insulin); interactions: Appendix 1 (antidiabetics)

Hepatic impairment section 6.1.1**Renal impairment** section 6.1.1**Pregnancy** section 6.1.1**Breast-feeding** section 6.1.1**Side-effects** see under Insulin**Licensed use** not licensed for use in children under 2 years**Indications and dose****Diabetes mellitus**

- By subcutaneous injection
Shortly before meals or when necessary shortly after meals, according to requirements
- By subcutaneous infusion, or intravenous injection, or intravenous infusion
According to requirements

Administration For intravenous infusion, dilute to a concentration of 0.1–1 unit/mL with Glucose 5% or Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

Humalog® (Lilly) [PoM]

Injection, insulin lispro (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £16.61; 5 × 3-mL cartridge (for *Autopen*® *Classic* or *HumaPen*®) = £28.31; 5 × 3-mL *Humalog*® *Kwik-Pen* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46

Counselling Show container to child or carer and confirm the expected version is dispensed

6.1.1.2 Intermediate- and long-acting insulins

When given by subcutaneous injection, intermediate- and long-acting insulins have an onset of action of approximately 1–2 hours, a maximal effect at 4–12 hours, and a duration of 16–35 hours. Some are given twice daily in conjunction with short-acting (soluble) insulin, and others are given once daily. Soluble insulin can be mixed with intermediate and long-acting insulins (except insulin detemir and insulin glargine), essentially retaining the properties of the two components, although there may be some blunting of the initial effect of the soluble insulin component (especially on mixing with protamine zinc insulin, see below).

Close monitoring of blood glucose is essential when introducing a change to the insulin regimen; the total daily dose as well as any concomitant treatment may need to be adjusted.

Isothane insulin is a suspension of insulin with protamine; it is of particular value for initiation of twice-daily insulin regimens. Isothane can be mixed with soluble insulin before injection but ready-mixed preparations may be more appropriate (**biphasic isophane insulin**, **biphasic insulin aspart**, or **biphasic insulin lispro**).

Insulin zinc suspension (30% amorphous, 70% crystalline) has a more prolonged duration of action.

Protamine zinc insulin is usually given once daily with short-acting (soluble) insulin. It has the drawback of binding with the soluble insulin when mixed in the same syringe and is now rarely used.

Insulin detemir and **insulin glargine** are long-acting human insulin analogues with a prolonged duration of action; insulin detemir is given once or twice daily and insulin glargine is given once daily. These long-acting insulins are ideal for once or twice daily dosing in a multiple injection regimen in combination with a short-acting insulin before meals. NICE (December 2002) has recommended that insulin glargine should be available as an option for patients with type 1 diabetes.

NICE (May 2009) has recommended that, if insulin is required in patients with type 2 diabetes, insulin detemir or insulin glargine may be considered for those:

- who require assistance with injecting insulin or
- whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia or
- who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs or
- who cannot use the device needed to inject isophane insulin.

INSULIN DETEMIR

(Recombinant human insulin analogue—long-acting)

Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)

Hepatic impairment section 6.1.1

Renal impairment section 6.1.1

Pregnancy section 6.1.1

Breast-feeding section 6.1.1

Side-effects see under Insulin (section 6.1.1.1)

Indications and dose

Diabetes mellitus

- By subcutaneous injection

Child over 2 years according to requirements

Levemir® (Novo Nordisk) (PoM)

Injection, insulin detemir (recombinant human insulin analogue) 100 units/mL, net price 5 × 3-mL cartridge (for *NovoPen®* devices) = £42.00; 5 × 3-mL *FlexPen®* prefilled disposable injection device (range 1–60 units, allowing 1-unit dosage adjustment) = £42.00; 5 × 3-mL *Levemir InnoLet®* prefilled disposable injection devices (range 1–50 units, allowing 1-unit dosage adjustment) = £44.85

Counselling Show container to child or carer and confirm the expected version is dispensed

INSULIN GLARGINE

(Recombinant human insulin analogue—long acting)

Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)

Hepatic impairment section 6.1.1

Renal impairment section 6.1.1

Pregnancy section 6.1.1

Breast-feeding section 6.1.1

Side-effects see under Insulin (section 6.1.1.1)

Indications and dose

Diabetes mellitus

- By subcutaneous injection

Child over 2 years according to requirements

Lantus® (Sanofi-Aventis) (PoM)

Injection, insulin glargine (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £30.68; 5 × 3-mL cartridge (for *ClikSTAR®* and *Autopen®* 24) = £41.50; 5 × 3-mL *Lantus SoloStar®* prefilled disposable injection devices (range 1–80 units, allowing 1-unit dosage adjustment) = £41.50

Note The *Scottish Medicines Consortium* (p. 3) has advised (March 2013) that insulin glargine is accepted for restricted use within NHS Scotland for the treatment of type 1 diabetes:

- in those who are at risk of or experience unacceptable frequency or severity of nocturnal hypoglycaemia on attempting to achieve better hypoglycaemic control during treatment with other insulins
- as a once daily insulin therapy for patients who require a carer to administer their insulin.

It is **not** recommended for routine use in patients with type 2 diabetes unless they suffer from recurrent episodes of hypoglycaemia or require assistance with their insulin injections.

Counselling Show container to child or carer and confirm the expected version is dispensed

INSULIN ZINC SUSPENSION

(Insulin Zinc Suspension (Mixed)—long acting)

A sterile neutral suspension of bovine insulin or of human insulin in the form of a complex obtained by the addition of a suitable zinc salt; consists of rhombohedral crystals (10–40 microns) and of particles of no uniform shape (not exceeding 2 microns)

Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)

Hepatic impairment section 6.1.1

Renal impairment section 6.1.1

Pregnancy section 6.1.1

Breast-feeding section 6.1.1

Side-effects see under Insulin (section 6.1.1.1)

Indications and dose

Diabetes mellitus

- By subcutaneous injection

According to requirements

▲ **Highly purified animal**

Hypurin® Bovine Lente (Wockhardt) (PoM)

Injection, insulin zinc suspension (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £27.72

Counselling Show container to child or carer and confirm the expected version is dispensed

ISOPHANE INSULIN

(Isophane Insulin Injection; Isophane Protamine Insulin Injection; Isophane Insulin (NPH)—intermediate acting)

A sterile suspension of bovine or porcine insulin or of human insulin in the form of a complex obtained by the addition of protamine sulfate or another suitable protamine

Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)**Hepatic impairment** section 6.1.1**Renal impairment** section 6.1.1**Pregnancy** section 6.1.1**Breast-feeding** section 6.1.1**Side-effects** see under Insulin (section 6.1.1.1); protamine may cause allergic reactions**Indications and dose****Diabetes mellitus**

- By subcutaneous injection

According to requirements

Highly purified animal**Counselling** Show container to child or carer and confirm the expected version is dispensed**Hypurin® Bovine Isophane** (Wockhardt) (PoM)**Injection**, isophane insulin (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £27.72; cartridges (for *Autopen® Classic*) 5 × 3 mL = £41.58**Hypurin® Porcine Isophane** (Wockhardt) (PoM)**Injection**, isophane insulin (porcine, highly purified) 100 units/mL. Net price 10-mL vial = £25.20; cartridges (for *Autopen® Classic*) 5 × 3 mL = £37.80**Human sequence****Counselling** Show container to child or carer and confirm the expected version is dispensed**Insulatard®** (Novo Nordisk) (PoM)**Injection**, isophane insulin (human, pyr) 100 units/mL. Net price 10-mL vial = £7.48; *Insulatard Penfill®* cartridge (for *Innovo®*, or *Novopen®* devices) 5 × 3 mL = £22.90; 5 × 3-mL *Insulatard InnoLet®* pre-filled disposable injection devices (range 1–50 units, allowing 1-unit dosage adjustment) = £20.40**Humulin I®** (Lilly) (PoM)**Injection**, isophane insulin (human, prb) 100 units/mL, net price 10-mL vial = £15.68; 5 × 3-mL cartridge (for *Autopen® Classic* or *HumaPen®*) = £19.08; 5 × 3-mL *Humulin 1 KwikPen®* pre-filled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £21.70**Insuman® Basal** (Sanofi-Aventis) (PoM)**Injection**, isophane insulin (human, crb) 100 units/mL, net price 5-mL vial = £5.61; 5 × 3-mL cartridge (for *KlikSTAR®* and *Autopen® 24*) = £17.50; 5 × 3-mL *Insuman® Basal Solostar®* pre-filled disposable injection devices (range 1–80 units, allowing 1-unit dosage adjustment) = £19.80**Mixed preparations**

See Biphasic Isophane Insulin (p. 363)

PROTAMINE ZINC INSULIN

(Protamine Zinc Insulin Injection—long acting)

A sterile suspension of insulin in the form of a complex obtained by the addition of a suitable protamine and zinc chloride; this preparation was included in BP 1980 but is not included in BP 1988

Cautions section 6.1.1; see also notes above; **interactions:** Appendix 1 (antidiabetics)**Hepatic impairment** section 6.1.1**Renal impairment** section 6.1.1**Pregnancy** section 6.1.1**Breast-feeding** section 6.1.1**Side-effects** see under Insulin (section 6.1.1.1); protamine may cause allergic reactions**Indications and dose****Diabetes mellitus**

- By subcutaneous injection

According to requirements

Hypurin® Bovine Protamine Zinc (Wockhardt) (PoM)**Injection**, protamine zinc insulin (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £27.72**Counselling** Show container to child or carer and confirm the expected version is dispensed**Biphasic insulins**

Biphasic insulins are pre-mixed insulin preparations containing various combinations of short-acting (soluble) or rapid-acting (analogue) insulin and an intermediate-acting insulin.

The percentage of short-acting insulin varies from 10% to 50%. These preparations should be administered by subcutaneous injection up to 15 minutes before or soon after a meal.

BIPHASIC INSULIN ASPART

(Intermediate-acting insulin)

Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)**Hepatic impairment** section 6.1.1**Renal impairment** section 6.1.1**Pregnancy** section 6.1.1**Breast-feeding** section 6.1.1**Side-effects** see under Insulin (section 6.1.1.1); protamine may cause allergic reactions**Indications and dose****Diabetes mellitus**

- By subcutaneous injection

Up to 10 minutes before or soon after a meal, according to requirements

NovoMix® 30 (Novo Nordisk) (PoM)**Injection**, biphasic insulin aspart (recombinant human insulin analogue), 30% insulin aspart, 70% insulin aspart protamine, 100 units/mL, net price 5 × 3-mL *Penfill®* cartridges (for *Innovo®* and *Novopen®* devices) = £28.79; 5 × 3-mL *FlexPen®* pre-filled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.89**Counselling** Show container to child or carer and confirm the expected version is dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)**BIPHASIC INSULIN LISPRO**

(Intermediate-acting insulin)

Cautions see section 6.1.1 and Insulin Lispro; **interactions:** Appendix 1 (antidiabetics)**Hepatic impairment** section 6.1.1**Renal impairment** section 6.1.1

Pregnancy section 6.1.1**Breast-feeding** section 6.1.1**Side-effects** see under Insulin (section 6.1.1.1); protamine may cause allergic reactions**Indications and dose****Diabetes mellitus**

- By subcutaneous injection

Up to 15 minutes before or soon after a meal, according to requirements

Humalog® Mix25 (Lilly) (PoM)

Injection, biphasic insulin lispro (recombinant human insulin analogue), 25% insulin lispro, 75% insulin lispro protamine, 100 units/mL, net price 10-mL vial = £16.61; 5 × 3-mL cartridge (for *Autopen® Classic* or *HumaPen®*) = £29.46; 5 × 3-mL *Humalog® Mix25 KwikPen* prefilled disposable injection devices (range 1–60 units allowing 1-unit dosage adjustment) = £30.98

Counselling Show container to child or carer and confirm the expected version is dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)

Humalog® Mix50 (Lilly) (PoM)

Injection, biphasic insulin lispro (recombinant human insulin analogue), 50% insulin lispro, 50% insulin lispro protamine, 100 units/mL, net price 5 × 3-mL cartridge (for *Autopen® Classic* or *HumaPen®*) = £29.46; 5 × 3-mL *Humalog® Mix50 KwikPen* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98

Counselling Show container to child or carer and confirm the expected version is dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)

BIPHASIC ISOPHANE INSULIN

(Biphasic Isophane Insulin Injection—intermediate acting)

A sterile buffered suspension of either porcine or human insulin complexed with protamine sulfate (or another suitable protamine) in a solution of insulin of the same species

Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)

Hepatic impairment section 6.1.1**Renal impairment** section 6.1.1**Pregnancy** section 6.1.1**Breast-feeding** section 6.1.1**Side-effects** see under Insulin (section 6.1.1.1); protamine may cause allergic reactions**Indications and dose****Diabetes mellitus**

- By subcutaneous injection

According to requirements

Highly purified animal

Counselling Show container to child or carer and confirm the expected version is dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)

Humulin® Porcine 30/70 Mix (Wockhardt) (PoM)

Injection, biphasic isophane insulin (porcine, highly purified), 30% soluble, 70% isophane, 100 units/mL, net price 10-mL vial = £25.20; cartridges (for *Autopen® Classic*) 5 × 3 mL = £37.80

Human sequence

Counselling Show container to child or carer and confirm the expected version is dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)

Humulin M3® (Lilly) (PoM)

Injection, biphasic isophane insulin (human, prb), 30% soluble, 70% isophane, 100 units/mL, net price 10-mL vial = £15.68; 5 × 3-mL cartridge (for *Autopen® Classic* or *HumaPen®*) = £19.08; 5 × 3-mL *Humulin M3 KwikPen®* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £21.70

Insuman® Comb 15 (Sanofi-Aventis) (PoM)

Injection, biphasic isophane insulin (human, crb), 15% soluble, 85% isophane, 100 units/mL, net price 5 × 3-mL cartridge (for *ClickSTAR®* and *Autopen® 24*) = £17.50

Insuman® Comb 25 (Sanofi-Aventis) (PoM)

Injection, biphasic isophane insulin (human, crb), 25% soluble, 75% isophane, 100 units/mL, net price 5-mL vial = £5.61; 5 × 3-mL cartridge (for *ClickSTAR®* and *Autopen® 24*) = £17.50; 5 × 3-mL *Insuman® Comb 25 SoloStar* prefilled disposable injection devices (range 1–80 units, allowing 1-unit dosage adjustment) = £19.80

Insuman® Comb 50 (Sanofi-Aventis) (PoM)

Injection, biphasic isophane insulin (human, crb), 50% soluble, 50% isophane, 100 units/mL, net price; 5 × 3-mL cartridge (for *ClickSTAR®* and *Autopen® 24*) = £17.50

6.1.1.3 Hypodermic equipment

Carers and children should be advised on the safe disposal of lancets, single-use syringes, and needles. Suitable arrangements for the safe disposal of contaminated waste must be made before these products are prescribed for patients who are carriers of infectious diseases.

Injection devices**Autopen®** (Owen Mumford)

Injection device, *Autopen® 24* (for use with Sanofi-Aventis 3-mL insulin cartridges), allowing 1-unit dosage adjustment, max. 21 units (single-unit version) or 2 unit dosage adjustment, max. 42 units (2 unit version), net price (both) = £16.47; *Autopen® Classic* (for use with Lilly and Wockhardt 3-mL insulin cartridges), allowing 1-unit dosage adjustment, max. 21 units (single-unit version) or 2 unit dosage adjustment, max. 42 units (2-unit version), net price (all) = £16.72

ClickSTAR® (Sanofi-Aventis)

Injection device, for use with *Lantus®*, *Apidra®*, and *Insuman®* 3-mL insulin cartridges; allowing 1-unit dose adjustment, max. 80 units, net price = £25.00

HumaPen® Luxura (Lilly)

Injection device, for use with *Humulin®* and *Humalog®* 3-mL cartridges; allowing 1-unit dosage adjustment, max. 60 units, net price = £26.82

HumaPen® Luxura HD (Lilly)

Injection device, for use with *Humulin®* and *Humalog®* 3-mL cartridges; allowing 0.5-unit dosage adjustment, max. 30 units, net price = £26.82

Humapen® Memoir (Lilly)

Injection device, for use with *Humalog*® 3-mL cartridges; allowing 1-unit dosage adjustment, max. 60 units, net price = £26.82

Injex® (Injex UK)

Needle-free insulin delivery device, for use with any 10-mL vial of insulin, allowing 1-unit dosage adjustment, max. 30 units, net price *starter set* (*Injex*® device, reset box, transporter, 9 x 10-mL vial adaptors, 165 ampoules) = £149.36; *4-month refill pack* (6 x 10-mL vial adaptors, 100 ampoules) = £24.47; *ampoule pack* (50 ampoules) = £12.28; *vial adaptor pack* (20 x 10-mL vial adaptors) = £12.23

Insulet® (European Pharma)

Needle-free insulin delivery device, for use with any 10-mL vial or 3-mL cartridge of insulin, allowing 1-unit dosage adjustment, max. 40 units, net price *starter set* (*InsuJet*® device, nozzle cap, nozzle and piston, 1 x 10-mL adaptor, 1 x 3-mL adaptor, 1 cartridge cap removal key) = £143.60, nozzle pack (15 nozzles) = £28.40, cartridge adaptor pack (15 adaptors) = £21.70, vial adaptor pack (15 adaptors) = £21.70

NovoPen® 4 (Novo Nordisk)

Injection device, for use with *Penfill*® 3-mL insulin cartridges; allowing 1-unit dosage adjustment, max. 60 units, net price = £26.86

NovoPen Echo® (Novo Nordisk)

Injection device, for use with *Penfill*® 3-mL insulin cartridges; allowing 0.5-unit dosage adjustment, max. 30 units, net price = £26.86

■ Lancets, needles, syringes, and accessories

Lancets, needles, syringes, and accessories are listed under Hypodermic Equipment in Part IXA of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 3 of the Scottish Drug Tariff).

The Drug Tariffs can be accessed online at: National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm Health and Personal Social Services for Northern Ireland Drug Tariff: www.dhsspsni.gov.uk/pas-tariff Scottish Drug Tariff: www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

6.1.2 Antidiabetic drugs**6.1.2.1 Sulfonylureas****6.1.2.2 Biguanides****6.1.2.3 Other antidiabetic drugs**

Oral antidiabetic drugs are used for the treatment of type 2 diabetes mellitus. They should be prescribed only if the child fails to respond adequately to restriction of energy and carbohydrate intake and an increase in physical activity. They should be used to augment the effect of diet and exercise, and not to replace them.

In children, type 2 diabetes does not usually occur until adolescence and information on the use of oral antidiabetic drugs in children is limited. Treatment with oral antidiabetic drugs should be initiated under specialist supervision **only**; the initial dose should be at the lower

end of the adult dose range and then adjusted according to response.

Metformin (section 6.1.2.2) is the oral antidiabetic drug of choice because there is most experience with this drug in children. If dietary changes and metformin do not control the diabetes adequately, either a sulfonylurea (section 6.1.2.1) or insulin (section 6.1.1) can be added.

Alternatively, oral therapy may be substituted with insulin.

When insulin is added to oral therapy, it is generally given at bedtime as isophane or long-acting insulin, and when insulin replaces an oral regimen it may be given as twice-daily injections of a biphasic insulin (or isophane insulin mixed with soluble insulin), or a multiple injection regimen. Weight gain and hypoglycaemia may be complications of insulin therapy but weight gain can be reduced if the insulin is given in combination with metformin.

Pregnancy and breast-feeding During pregnancy, women with *pre-existing diabetes* can be treated with metformin [unlicensed use], either alone or in combination with insulin (section 6.1.1). Metformin can be continued, or glibenclamide resumed, during breast-feeding for those with pre-existing diabetes. Women with *gestational diabetes* may be treated, with or without concomitant insulin (section 6.1.1), with glibenclamide from 11 weeks gestation (after organogenesis) [unlicensed use] or with metformin [unlicensed use]. Women with gestational diabetes should discontinue hypoglycaemic treatment after giving birth.

Other oral hypoglycaemic drugs are contra-indicated in pregnancy and breast-feeding.

6.1.2.1 Sulfonylureas

The sulfonylureas are not the first choice oral antidiabetics in children. They act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action. All can cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulfonylurea-induced hypoglycaemia can persist for many hours and must always be treated in hospital.

Sulfonylureas are considered for children in whom metformin is contra-indicated or not tolerated. Several sulfonylureas are available but experience in children is limited; choice is determined by side-effects and the duration of action as well as the child's age and renal function. Glibenclamide, a long-acting sulfonylurea, is associated with a greater risk of hypoglycaemia and for this reason is generally avoided in children. Shorter-acting alternatives, such as **tolbutamide**, may be preferred.

Insulin therapy should be instituted temporarily during intercurrent illness (such as coma, infection, and trauma). Sulfonylureas should be omitted on the morning of surgery; insulin is often required because of the ensuing hyperglycaemia in these circumstances.

Sulfonylureas can be useful in the management of certain forms of diabetes that result from genetic defects of beta-cell function; there is most experience with gliclazide.

Cautions Sulfonylureas encourage weight gain and should be prescribed only if poor control and symptoms persist despite adequate attempts at dieting; metformin (section 6.1.2.2) is considered the drug of choice in children. Caution is needed in children with G6PD deficiency (section 9.1.5).

Contra-indications Sulfonylureas should be avoided where possible in acute porphyria (section 9.8.2). Sulfonylureas are contra-indicated in the presence of ketoacidosis.

Hepatic impairment Sulfonylureas should be avoided or a reduced dose should be used in severe hepatic impairment, because there is an increased risk of hypoglycaemia. Jaundice may occur.

Renal impairment Sulfonylureas should be used with care in those with mild to moderate renal impairment, because of the hazard of hypoglycaemia; they should be avoided where possible in severe renal impairment. If necessary, the short-acting drug tolbutamide can be used in renal impairment, as can gliclazide which is principally metabolised in the liver, but careful monitoring of blood-glucose concentration is essential; care is required to use the lowest dose that adequately controls blood glucose.

Pregnancy The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia; however, glibenclamide can be used during the second and third trimesters of pregnancy in women with gestational diabetes, see section 6.1.2.

Breast-feeding The use of sulfonylureas (except glibenclamide [unlicensed use], see section 6.1.2) in breast-feeding should be avoided because there is a theoretical possibility of hypoglycaemia in the infant.

Side-effects Side-effects of sulfonylureas are generally mild and infrequent and include gastro-intestinal disturbances such as nausea, vomiting, diarrhoea and constipation.

Sulfonylureas can occasionally cause a disturbance in liver function, which rarely leads to cholestatic jaundice, hepatitis, and hepatic failure. Hypersensitivity reactions can occur, usually in the first 6–8 weeks of therapy. They consist mainly of allergic skin reactions which progress rarely to erythema multiforme or exfoliative dermatitis, fever, and jaundice; photosensitivity has rarely been reported with glipizide. Blood disorders are also rare but include leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, and aplastic anaemia.

GLIBENCLAMIDE

Cautions see notes above; **interactions:** Appendix 1 (antidiabetics)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use not licensed for use in children

Indications and dose

Type 2 diabetes mellitus, maturity-onset diabetes of the young (specialist management only, see notes above)

• By mouth

Child 12–18 years initially 2.5 mg daily with or immediately after breakfast, adjusted according to response, max. 15 mg daily

Glibenclamide (Non-proprietary) (PoM)

Tablets, glibenclamide 2.5 mg, net price 28-tab pack = £18.27; 5 mg, 28-tab pack = 97p

GLICLAZIDE

Cautions see notes above; **interactions:** Appendix 1 (antidiabetics)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use not licensed for use in children

Indications and dose

Type 2 diabetes mellitus, maturity-onset diabetes of the young (specialist management only, see notes above)

• By mouth

Child 12–18 years initially 20 mg once daily with breakfast, adjusted according to response; up to 160 mg as a single dose; max. 160 mg twice daily

Gliclazide (Non-proprietary) (PoM)

Tablets, gliclazide 40 mg, net price 28-tab pack = £3.36; 80 mg, 28-tab pack = £1.04, 60-tab pack = £2.23

Brands include Zicon®

Diamicon® (Servier) (PoM)

Tablets, scored, gliclazide 80 mg, net price 60-tab pack = £4.38

TOLBUTAMIDE

Cautions see notes above; **interactions:** Appendix 1 (antidiabetics)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also headache, tinnitus

Licensed use not licensed for use in children

Indications and dose

Type 2 diabetes mellitus (see notes above), specialist management only

• By mouth

Child 12–18 years 0.5–1.5 g (max. 2 g) daily in divided doses with or immediately after meals or as a single dose with or immediately after breakfast

Tolbutamide (Non-proprietary) (PoM)

Tablets, tolbutamide 500 mg. Net price 28-tab pack = £22.64

6.1.2.2 Biguanides

Metformin, the only available biguanide, has a different mode of action from the sulfonylureas, and is not interchangeable with them. It exerts its effect mainly by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose; since it acts only in the presence of endogenous insulin it is effective only if there are some residual functioning pancreatic islet cells.

Metformin is the drug of first choice in children with type 2 diabetes, in whom strict dieting has failed to control diabetes. When the combination of strict diet and metformin treatment fails, other options to be considered under specialist management only, include:

- combining with insulin (section 6.1.1) but weight gain and hypoglycaemia can be problems (weight gain minimised if insulin given at night);
- combining with a sulfonylurea (section 6.1.2.1) (reports of increased hazard with this combination remain unconfirmed).

Insulin treatment is almost always required in medical and surgical emergencies; insulin should also be substituted before elective surgery (omit metformin on the morning of surgery and give insulin if required).

Hypoglycaemia does not usually occur with metformin; other advantages are the lower incidence of weight gain and lower plasma-insulin concentration. It does not exert a hypoglycaemic action in non-diabetic subjects unless given in overdose.

Gastro-intestinal side-effects are initially common with metformin, and may persist in some children, particularly when high doses are given. A slow increase in dose may improve tolerability.

Very rarely, metformin can provoke lactic acidosis which is most likely to occur in children with renal impairment, see Lactic Acidosis p. 366.

METFORMIN HYDROCHLORIDE

Cautions see notes above; determine renal function before treatment and at least annually (at least twice a year in patients with additional risk factors for renal impairment, or if deterioration suspected); **interactions:** Appendix 1 (antidiabetics)

Lactic acidosis Use with caution in renal impairment—increased risk of lactic acidosis; avoid in significant renal impairment. Withdraw or interrupt treatment in those at risk of tissue hypoxia or sudden deterioration in renal function, such as those with dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure, or hepatic impairment

Contra-indications ketoacidosis; use of general anaesthesia (suspend metformin on the morning of surgery and restart when renal function returns to baseline)

Iodine-containing X-ray contrast media Intravascular administration of iodinated contrast agents can cause renal failure, which can increase the risk of lactic acidosis with metformin—see Lactic Acidosis above. Suspend metformin prior to the test; restart no earlier than 48 hours after the test if renal function has returned to baseline

Hepatic impairment withdraw if tissue hypoxia likely

Renal impairment see under Cautions

Pregnancy used in pregnancy for both pre-existing and gestational diabetes—see also Pregnancy and Breast-feeding, p. 364

Breast-feeding may be used during breast-feeding—see also Pregnancy and Breast-feeding, p. 364

Side-effects anorexia, nausea, vomiting, diarrhoea (usually transient), abdominal pain, taste disturbance; rarely lactic acidosis (withdraw treatment), decreased vitamin-B₁₂ absorption, erythema, pruritus and urticaria; hepatitis also reported

Licensed use not licensed for use in children under 10 years

Indications and dose

Diabetes mellitus (see notes above) specialist supervision only

• By mouth

Child 8–10 years initially 200 mg once daily adjusted according to response at intervals of at least 1 week; max. 2 g daily in 2–3 divided doses

Child 10–18 years initially 500 mg once daily adjusted according to response at intervals of at least 1 week; max. 2 g daily in 2–3 divided doses

Metformin (Non-proprietary) (PoM)

Tablets, coated, metformin hydrochloride 500 mg, net price 28-tab pack = 87p, 84-tab pack = £1.00; 850 mg, 56-tab pack = £1.36. Label: 21

Oral solution, sugar-free, metformin hydrochloride 500 mg/5 mL, net price 100 mL = £40.50. Label: 21

Glucophage® (Merck Serono) (PoM)

Tablets, f/c, metformin hydrochloride 500 mg, net price 84-tab pack = £2.88; 850 mg, 56-tab pack = £3.20. Label: 21

Oral powder, sugar-free, metformin hydrochloride 500 mg/sachet, net price 30-sachet pack = £3.29, 60-sachet pack = £6.58; 1 g/sachet, 30-sachet pack = £6.58, 60-sachet pack = £13.16. Label: 13, 21, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling The contents of each sachet should be mixed with 150 mL of water and taken immediately

The Scottish Medicines Consortium (p. 3) has advised (March 2010) that *Glucophage*® oral powder is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients who are unable to swallow the solid dosage form.

6.1.2.3 Other antidiabetic drugs

There is little experience of the use of **acarbose** in children. It has been used in older children; therapy should be initiated by an appropriate expert.

The use of nateglinide in combination with a sulfonylurea is generally reserved for the management of some subtypes of diabetes resulting from genetic defects of beta-cell function or other syndromes of diabetes and requires specialist management.

6.1.3 Diabetic ketoacidosis

The management of diabetic ketoacidosis involves the replacement of fluid and electrolytes and the administration of insulin. Guidelines for the Management of Diabetic Ketoacidosis, published by the British Society of Paediatric Endocrinology and Diabetes¹, should be followed. Clinically well children with mild ketoacidosis who are dehydrated up to 5% usually respond to oral rehydration and subcutaneous insulin. For those who do

1. Available at www.bsped.org.uk

not respond, or are clinically unwell, or are dehydrated by more than 5%, insulin and replacement fluids are best given by intravenous infusion.

- To restore circulating volume for children in *shock*, give 10 mL/kg **sodium chloride 0.9%** as a rapid infusion, repeat as necessary up to a maximum of 30 mL/kg.
- Further fluid should be given by intravenous infusion at a rate that replaces deficit and provides maintenance over 48 hours; initially use **sodium chloride 0.9%**, changing to **sodium chloride 0.45%** and **glucose 5%** after 12 hours if response is adequate and plasma-sodium concentration is stable.
- Include **potassium chloride** in the fluids unless anuria is suspected, adjust according to plasma-potassium concentration.
- Insulin infusion is necessary to switch off ketogenesis and reverse acidosis; it should not be started until at least 1 hour after the start of intravenous rehydration fluids.
- **Soluble insulin** should be diluted (and **mixed thoroughly**) with **sodium chloride 0.9%** intravenous infusion to a concentration of 1 unit/mL and infused at a rate of 0.1 units/kg/hour.
- **Sodium bicarbonate** infusion (1.26% or 2.74%) is rarely necessary and is used only in cases of extreme acidosis (blood pH less than 6.9) and shock, since the acid-base disturbance is normally corrected by treatment with insulin.
- Once blood glucose falls to 14 mmol/litre, **glucose intravenous infusion 5% or 10%** should be added to the fluids.
- The insulin infusion rate can be reduced to no less than 0.05 units/kg/hour when blood-glucose concentration has fallen to 14 mmol/litre and blood pH is greater than 7.3 and a glucose infusion has been started (see above); it is continued until the child is ready to take food by mouth. Subcutaneous insulin can then be started.
- The insulin infusion should not be stopped until 1 hour after starting subcutaneous soluble or long-acting insulin, or 10 minutes after starting subcutaneous insulin aspart, or insulin glulisine, or insulin lispro.

Hyperosmolar hyperglycaemic state or hyperosmolar hyperglycaemic nonketotic coma occurs rarely in children. Treatment is similar to that of diabetic ketoacidosis, although lower rates of insulin infusion and slower rehydration may be required.

6.1.4 Treatment of hypoglycaemia

Prompt treatment of hypoglycaemia in children from any cause is essential as severe hypoglycaemia may cause subsequent neurological damage. Hyperinsulinism, fatty acid oxidation disorders and glycogen storage disease are less common causes of acute hypoglycaemia in children.

Initially glucose 10–20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps. Approximately 10 g of glucose is available from non-diet versions of *Lucozade® Energy Original* 55 mL, *Coca-Cola®* 100 mL, and *Ribena® Blackcurrant* 19 mL (to be

diluted), 2 teaspoons of sugar, and also from 3 sugar lumps¹. If necessary this can be repeated in 10–15 minutes. After initial treatment, a snack providing sustained availability of carbohydrate (e.g. a sandwich, fruit, milk, or biscuits) or the next meal, if it is due, can prevent blood-glucose concentration from falling again.

Hypoglycaemia which causes unconsciousness or seizures is an emergency. **Glucagon**, a polypeptide hormone produced by the alpha cells of the islets of Langerhans, increases blood-glucose concentration by mobilising glycogen stored in the liver. In hypoglycaemia, if sugar cannot be given by mouth, glucagon can be given by injection. Carbohydrates should be given as soon as possible to restore liver glycogen; glucagon is not appropriate for chronic hypoglycaemia. Glucagon can be issued to parents or carers of insulin-treated children for emergency use in hypoglycaemic attacks. It is often advisable to prescribe it on an 'if necessary' basis for hospitalised insulin-treated children, so that it can be given rapidly by the nurses during a hypoglycaemic emergency. If not effective in 10 minutes intravenous glucose should be given.

Alternatively, 5 mL/kg of glucose intravenous infusion 10% (500 mg/kg of glucose) (section 9.2.2) can be given intravenously into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs. Glucose intravenous infusion 50% is **not** recommended, as it is very viscous and hypertonic. Close monitoring is necessary, particularly in the case of an overdose with a long-acting insulin because further administration of glucose may be required. Children whose hypoglycaemia is caused by an oral antidiabetic drug should be transferred to hospital because the hypoglycaemic effects of these drugs can persist for many hours.

Glucagon is not effective in the treatment of hypoglycaemia due to fatty acid oxidation or glycogen storage disorders.

Neonatal hypoglycaemia Neonatal hypoglycaemia at birth is treated with **glucose intravenous infusion 10%** given at a rate of 5 mL/kg/hour. An initial dose of 2.5 mL/kg over 5 minutes may be required if hypoglycaemia is severe enough to cause loss of consciousness or seizures. Mild asymptomatic persistent hypoglycaemia may respond to a single dose of **glucagon**. Glucagon has also been used in the short-term management of endogenous hyperinsulinism.

GLUCAGON

Cautions see notes above, insulinoma, glucagonoma; ineffective in chronic hypoglycaemia, starvation, and adrenal insufficiency; delayed hypoglycaemia when used as a diagnostic test—deaths reported (ensure a meal is eaten before discharge)

Contra-indications pheochromocytoma

Side-effects nausea, vomiting, diarrhoea, hypokalaemia, rarely hypersensitivity reactions

Licensed use unlicensed for growth hormone test and hyperinsulinism; intravenous route unlicensed

1. Proprietary products of quick-acting carbohydrate (e.g. *GlucoGel®*, *DextroGel®*, *GSF-Syrup®*, *Rapilose®* gel) are available on prescription for the patient to keep to hand in case of hypoglycaemia

Indications and dose**Hypoglycaemia associated with diabetes**

- By subcutaneous, intramuscular, or intravenous injection

Neonate 20 micrograms/kg

Child 1 month–2 years 500 micrograms

Child 2–18 years, body-weight less than 25 kg 500 micrograms; **body-weight over 25 kg** 1 mg

Endogenous hyperinsulinism

- By intramuscular or intravenous injection

Neonate 200 micrograms/kg (max. 1 mg) as a single dose

Child 1 month–2 years 1 mg as a single dose

- By continuous intravenous infusion

Neonate 1–18 micrograms/kg/hour, adjusted according to response (max. 50 micrograms/kg/hour)

Child 1 month–2 years 1–10 micrograms/kg/hour, increased if necessary

Administration Do not add to infusion fluids containing calcium—precipitation may occur

Diagnosis of growth hormone secretion specialist centre only (section 6.5.1)

- By intramuscular injection

Child 1 month–18 years 100 micrograms/kg (max. 1 mg) as a single dose; dose may vary, consult local guidelines

Beta-blocker poisoning, see p. 29

Note 1 unit of glucagon = 1 mg of glucagon

¹GlucaGen® HypoKit (Novo Nordisk) (POM)

Injection, powder for reconstitution, glucagon (rys) as hydrochloride with lactose, net price 1-mg vial with prefilled syringe containing water for injection = £11.52

Chronic hypoglycaemia

Diazoxide is useful in the management of chronic hypoglycaemia due to excessive insulin secretion, either from a tumour involving the islets of Langerhans or from persisting hyperinsulinaemic hypoglycaemia of infancy (nesidioblastosis, see also glucagon above). Diazoxide has no place in the management of acute hypoglycaemia. **Chlorothiazide** 3–5 mg/kg twice daily (section 2.2.1) reduces diazoxide-induced sodium and water retention and has the added benefit of potentiating the glycaemic effect of diazoxide.

If diazoxide and chlorothiazide fail to suppress excessive glucose requirements in chronic hypoglycaemia then **octreotide** or **nifedipine** (section 2.6.2) can be added. Octreotide suppresses secretion of growth hormone, but growth is unlikely to be affected in the long term.

DIAZOXIDE

Cautions impaired cardiac or cerebral circulation; heart failure; aortic coarctation; aortic stenosis; arteriovenous shunt; monitor blood pressure; hyperuricaemia; during prolonged use monitor white cell and platelet count, and regularly assess growth, bone,

and psychological development; **interactions:**

Appendix 1 (diazoxide)

Renal impairment dose reduction may be required

Pregnancy use only if essential; alopecia and hypertrichosis reported in neonates with prolonged use; may inhibit uterine activity in labour

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, abdominal pain, diarrhoea, constipation, ileus, pancreatitis, anorexia (prolonged use), taste disturbance, bleeding, heart failure, hypotension, pulmonary hypertension, dyspnoea, extrapyramidal effects, headache, dizziness, galactorrhoea, hyperglycaemia, decreased libido, leucopenia, thrombocytopenia, anaemia, eosinophilia, hyperosmolar non-ketotic coma, raised serum creatinine and urea, reversible nephritic syndrome, sodium and fluid retention, hyperuricaemia (prolonged use), musculoskeletal pain, visual disturbances, transient cataracts, lacrimation, tinnitus, voice changes (prolonged use), hypertrichosis, pruritus, dermatitis, lichenoid eruption

Indications and dose**Chronic intractable hypoglycaemia**

- By mouth

Neonate initially 5 mg/kg twice daily to establish response, adjust dose according to response; usual maintenance dose 1.5–3 mg/kg 2–3 times daily; up to 7 mg/kg 3 times daily may be required in some cases, higher doses unlikely to be beneficial

Child 1 month–18 years initially 1.7 mg/kg 3 times daily then adjusted according to response; usual maintenance dose 1.5–3 mg/kg 2–3 times daily; up to 5 mg/kg 3 times daily may be required in some cases, higher doses unlikely to be beneficial

Resistant hypertension section 2.5.1.1**Eudemine®** (PharSafer) (POM)

Tablets, diazoxide 50 mg, net price 100 = £46.45

OCTREOTIDE

Cautions avoid abrupt withdrawal of short-acting octreotide—see Side-effects below; in insulinoma (risk of increased depth and duration of hypoglycaemia—monitor closely when initiating treatment and changing doses); diabetes mellitus (antidiabetic requirements may be reduced); monitor thyroid function on long-term therapy; monitor liver function; **interactions:** Appendix 1 (octreotide)

Pregnancy possible effect on fetal growth, avoid unless benefit outweighs risk; effective contraception required during treatment

Breast-feeding avoid unless essential—present in milk in animal studies

Side-effects anorexia, nausea, vomiting, abdominal pain, bloating, flatulence, diarrhoea, constipation, and steatorrhoea (administer between meals or at bedtime to reduce gastro-intestinal side-effects); bradycardia, dyspnoea, headache, dizziness; postprandial glucose tolerance may be impaired, rarely persistent hyperglycaemia with chronic administration; hypoglycaemia has also been reported; reduced gall bladder motility and bile flow; gallstones reported after long-term treatment; abrupt withdrawal of subcutaneous octreotide is associated with biliary colic and pan-

¹ (POM) restriction does not apply where administration is for saving life in emergency

creatitis; rash, alopecia; pain and irritation at injection site—sites should be rotated; *rarely* pancreatitis shortly after administration; hepatitis also reported

Licensed use not licensed in children

Indications and dose

Persistent hyperinsulinaemic hypoglycaemia unresponsive to diazoxide and glucose

- By subcutaneous injection

Neonate initially 2–5 micrograms/kg every 6–8 hours, adjusted according to response; up to 7 micrograms/kg every 4 hours may rarely be required

Child 1 month–18 years initially 1–2 micrograms/kg every 4–6 hours, dose adjusted according to response; up to 7 micrograms/kg every 4 hours may rarely be required

Bleeding from oesophageal or gastric varices

- By continuous intravenous infusion

Child 1 month–18 years 1 microgram/kg/hour, higher doses may be required initially; when no active bleeding reduce dose over 24 hours; usual max. 50 micrograms/hour

Administration for intravenous infusion, dilute with Sodium Chloride 0.9% to a concentration of 10–50%

Sandostatatin® (Novartis) (POM)

Injection, octreotide (as acetate) 50 micrograms/mL, net price 1-mL amp = £2.97; 100 micrograms/mL, 1-mL amp = £5.59; 200 micrograms/mL 5-mL vial = £55.73; 500 micrograms/mL, 1-mL amp = £27.09

6.1.5 Treatment of diabetic nephropathy and neuropathy

Diabetic nephropathy

Regular review of diabetic children over 12 years of age should include an annual test for microalbuminuria (the earliest sign of nephropathy). If reagent strip tests (*Micral-Test II®* (JMS) or *Microbumintest®* (JMS)) are used and prove positive, the result should be confirmed by laboratory analysis of a urine sample. Microalbuminuria can occur transiently during puberty; if it persists (at least 3 positive tests) treatment with an ACE inhibitor (section 2.5.5.1) or an angiotensin-II receptor antagonist (section 2.5.5.2) under specialist guidance should be considered; to minimise the risk of renal deterioration, blood pressure should be carefully controlled (section 2.5).

ACE inhibitors can potentiate the hypoglycaemic effect of insulin and oral antidiabetic drugs; this effect is more likely during the first weeks of combined treatment and in children with renal impairment.

For the treatment of hypertension in diabetes, see section 2.5.

Diabetic neuropathy

Clinical neuropathy is rare in children whose diabetes is well controlled.

6.1.6 Diagnostic and monitoring devices for diabetes mellitus

Blood monitoring

Blood **glucose** monitoring using a meter gives a direct measure of the glucose concentration at the time of the test and can detect hypoglycaemia as well as hyperglycaemia. Carers and children should be properly trained in the use of blood glucose monitoring systems and the appropriate action to take on the results obtained. Inadequate understanding of the normal fluctuations in blood glucose can lead to confusion and inappropriate action.

Children using multiple injection regimens should understand how to adjust their insulin dose according to their carbohydrate intake. With fixed-dose insulin regimens, the carbohydrate intake needs to be regulated, and should be distributed throughout the day to match the insulin regimen.

Note In the UK blood-glucose concentration is expressed in mmol/litre and Diabetes UK advises that these units should be used for self-monitoring of blood glucose. In other European countries units of mg/100 mL (or mg/dL) are commonly used.

It is advisable to check that the meter is pre-set in the correct units.

If the blood glucose level is high or if the child is unwell, blood **ketones** should be measured according to local guidelines in order to detect diabetic ketoacidosis (section 6.1.3). Children and their carers should be trained in the use of blood ketone monitoring systems and to take appropriate action on the results obtained, including when to seek medical attention.

Urinalysis

Reagent strips are available for measuring glucose in the urine. It is rarely necessary for children to test themselves for ketones unless they become unwell—see also Blood Monitoring, p. 369.

Microalbuminuria can be detected with *Micral-Test II®* (JMS) but this should be followed by confirmation in the laboratory, since false positive results are common.

Glucose

Diabur-Test 5000® (Roche Diagnostics)

Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £2.87

Diastix® (Bayer Diabetes Care)

Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £2.78

Medi-Test® Glucose (BHR)

Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £2.33

Mission® Glucose (Spirit)

Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £2.29

Ketones

Ketostix® (Bayer Diabetes Care)

Reagent strips, for detection of ketones in urine. Net price 50-strip pack = £3.03

Meters and test strips

Meter (all ¹)	Type of monitoring	Compatible test strips	Test strip net price	Sensitivity range (mmol/litre)	Manufacturer
Accu-Chek [®] Active ¹	Blood glucose	Active [®]	50-strip pack = £9.95	0.6–33.3	Roche Diagnostics
Accu-Chek [®] Advantage ¹	Blood glucose	Advantage Plus [®]	50-strip pack = £15.89	0.6–33.3	Roche Diagnostics
Accu-Chek [®] Aviva	Blood glucose	Aviva [®]	50-strip pack = £15.59	0.6–33.3	Roche Diagnostics
Accu-Chek [®] Aviva Expert	Blood glucose	Aviva [®]	50-strip pack = £15.59	0.6–33.3	Roche Diagnostics
Accu-Chek [®] Compact Plus ¹	Blood glucose	Compact [®]	3 × 17-strip pack = £16.01	0.6–33.3	Roche Diagnostics
Accu-Chek [®] Mobile	Blood glucose	Mobile [®]	100 tests = £31.90	0.3–33.3	Roche Diagnostics
Accu-Chek [®] Aviva Nano	Blood glucose	Aviva	50-strip pack = £15.59	0.6–33.3	Roche Diagnostics
BGStar ^{®2}	Blood glucose	BGStar [®]	50-strip pack = £14.73	1.1–33.3	Sanofi
Breeze 2 [®]	Blood glucose	Breeze 2 [®]	5 × 10-disc pack = £14.87	0.6–33.3	Bayer Diabetes Care
CareSens N ^{®2}	Blood glucose	CareSens N [®]	50-strip pack = £12.75	1.1–33.3	Spirit Healthcare
Contour [®]	Blood glucose	Contour [®] Formerly Ascensia [®] Microfill	50-strip pack = £15.11	0.6–33.3	Bayer Diabetes Care
Contour [®] XT	Blood glucose	Contour [®] Next	50-strip pack = £15.04	0.6–33.3	Bayer Diabetes Care
Element [®]	Blood glucose	Element [®]	50-strip pack = £9.89	0.55–33.3	Neon Diagnostics
FreeStyle ^{®1}	Blood glucose	FreeStyle [®]	50-strip pack = £15.60	1.1–27.8	Abbott
FreeStyle Freedom ^{®1}	Blood glucose	FreeStyle [®]	50-strip pack = £15.60	1.1–27.8	Abbott
FreeStyle Freedom Lite [®]	Blood glucose	FreeStyle Lite [®]	50-strip pack = £15.60	1.1–27.8	Abbott
FreeStyle InsuLinx [®]	Blood glucose	FreeStyle Lite [®]	50-strip pack = £15.60	1.1–27.8	Abbott
FreeStyle Lite [®]	Blood glucose	FreeStyle Lite [®]	50-strip pack = £15.60	1.1–27.8	Abbott
FreeStyle Mini ^{®1}	Blood glucose	FreeStyle [®]	50-strip pack = £15.60	1.1–27.8	Abbott
FreeStyle Optium [®]	Blood glucose	FreeStyle Optium [®]	50-strip pack = £15.50	1.1–27.8	Abbott
	Blood ketones	FreeStyle Optium [®] β-ketone	10-strip pack = £20.86	0–8.0	Abbott
FreeStyle Optium Neo [®]	Blood glucose	FreeStyle Optium [®]	50-strip pack = £15.50	1.1–27.8	Abbott
	Blood ketones	FreeStyle Optium [®] β-ketone	10-strip pack = £20.86	0–8.0	Abbott
GlucoDock [®] module (for use with iPhone [®] , iPod touch [®] , or iPad [®])	Blood glucose	GlucoDock [®]	50-strip pack = £14.90	1.1–33.3	Medisana
GlucoLab [®]	Blood glucose	GlucoLab [®]	50-strip pack = £9.89	0.55–33.3	Neon Diagnostics
GlucoMen [®] Glyco ¹	Blood glucose	GlucoMen [®]	50-strip pack = £14.59	1.1–33.3	Menarini Diagnostics
GlucoMen [®] GM	Blood glucose	GlucoMen [®] GM	50-strip pack = £19.95	0.6–33.3	Menarini Diagnostics

1. Meter no longer available

2. Free of charge from diabetes healthcare professionals

Meter (all )	Type of monitoring	Compatible test strips	Test strip net price	Sensitivity range (mmol/litre)	Manufacturer
GlucoMen [®] LX	Blood glucose	GlucoMen [®] LX Sensor	50-strip pack = £15.39	1.1–33.3	Menarini Diagnostics
GlucoMen [®] LX Plus	Blood glucose	GlucoMen [®] LX Sensor	50-strip pack = £15.39	1.1–33.3	Menarini Diagnostics
	Blood ketones	GlucoMen [®] LX Ketone	10-strip pack = £20.57	0–0.8	Menarini Diagnostics
GlucoMen [®] PC ¹	Blood glucose	GlucoMen [®]	50-strip pack = £14.59	1.1–33.3	Menarini Diagnostics
GlucoMen [®] Visio	Blood glucose	GlucoMen [®] Visio Sensor	50-strip pack = £15.50	1.1–33.3	Menarini Diagnostics
GlucoRx ^{®2}	Blood glucose	GlucoRx [®]	50-strip pack = £9.45	1.1–33.3	GlucoRx
GlucoRx Nexus ^{®2}	Blood glucose	GlucoRx Nexus [®]	50-strip pack = £9.95	1.1–33.3	GlucoRx
Glucotrend ^{®1}	Blood glucose	Active [®]	50-strip pack = £9.95	0.6–33.3	Roche Diagnostics
iBGStar [®]	Blood glucose	BGStar [®]	50-strip pack = £14.73	1.1–33.3	Sanofi
IME-DC [®]	Blood glucose	IME-DC [®]	50-strip pack = £14.10	1.1–33.3	Arctic Medical
Mendor Discreet [®]	Blood glucose	Mendor Discreet [®]	50-strip pack = £14.75	1.1–33.3	Merck Serono
Microdot ^{®+2}	Blood glucose	Microdot ^{®+}	50-strip pack = £9.99	1.1–29.2	Cambridge Sensors
MyGlucoHealth [®]	Blood glucose	MyGlucoHealth [®]	50-strip pack = £15.50	0.6–33.3	Entra Health
Omnitest ^{®3}	Blood glucose	Omnitest ^{®3}	50-strip pack = £9.89	0.6–33.3	B. Braun
One Touch Ultra ^{®1}	Blood glucose	One Touch Ultra [®]	50-strip pack = £11.99	1.1–33.3	LifeScan
One Touch Ultra 2 ^{®2}	Blood glucose	One Touch Ultra [®]	50-strip pack = £11.99	1.1–33.3	LifeScan
One Touch UltraEasy ^{®2}	Blood glucose	One Touch Ultra [®]	50-strip pack = £11.99	1.1–33.3	LifeScan
One Touch UltraSmart ^{®2}	Blood glucose	One Touch Ultra [®]	50-strip pack = £11.99	1.1–33.3	LifeScan
One Touch VerioPro ^{®2}	Blood glucose	One Touch [®] Verio	50-strip pack = £14.99	1.1–33.3	LifeScan
One Touch [®] Vita ²	Blood glucose	One Touch [®] Vita	50-strip pack = £15.07	1.1–33.3	LifeScan
SD CodeFree [®]	Blood glucose	SD CodeFree [®]	50-strip pack = £6.99	0.6–33.3	SD Biosensor
Sensocard Plus ^{®1}	Blood glucose	Sensocard [®]	50-strip pack = £16.30	1.1–33.3	BBI Healthcare
SuperCheck2 ^{®2}	Blood glucose	SuperCheck2 [®]	50-strip pack = £8.49	1.1–33.3	Apollo Medical
TRUEone [®]	Blood glucose	All-in-one test strips and meter	50-strip pack with meter = £14.99	1.1–33.3	Nipro Diagnostics
TRUEresult ^{®2}	Blood glucose	TRUEresult [®]	50-strip pack = £14.99	1.1–33.3	Nipro Diagnostics
TRUEresult twist ^{®2}	Blood glucose	TRUEresult [®]	50-strip pack = £14.99	1.1–33.3	Nipro Diagnostics
TRUEtrack [®]	Blood glucose	TRUEtrack [®]	50-strip pack = £14.99	1.1–33.3	Nipro Diagnostics
TRUEyou mini [®]	Blood glucose	TRUEyou [®]	50-strip pack = £9.92	1.1–33.3	Nipro Diagnostics
WaveSense JAZZ ^{®2}	Blood glucose	WaveSense JAZZ [®]	50-strip pack = £9.87	1.1–33.3	AgaMatrix

1. Meter no longer available

2. Free of charge from diabetes healthcare professionals

Mission® Ketone (Spirit)

Reagent strips, for detection of ketones in urine. Net price 50-strip pack = £2.50


■ **Protein****Albustix®** (Siemens)

Reagent strips, for detection of protein in urine. Net price 50-strip pack = £4.10


Medi-Test® Protein 2 (BHR)

Reagent strips, for detection of protein in urine. Net price 50-strip pack = £3.27

■ **Other reagent strips available for urinalysis include:**

Combur-3 Test®  (glucose and protein—Roche Diagnostics),


Clinitek Microalbumin®  (albumin and creatinine—Siemens),

Ketodiastix®  (glucose and ketones—Bayer Diagnostics),

Medi-Test Combi 2®  (glucose and protein—BHR),

Micral-Test II®  (albumin—Roche Diagnostics),

Microalbustix®  (albumin and creatinine—Siemens),

Uristix®  (glucose and protein—Siemens)

Oral glucose tolerance test

The oral glucose tolerance test is used mainly for diagnosis of impaired glucose tolerance; it is not recommended or necessary for routine diagnostic use when severe symptoms of hyperglycaemia are present. However, it is used for the investigation of insulin resistance, glycogen storage disease, and excessive growth hormone secretion. In children who have less severe symptoms and blood-glucose concentrations that do not establish or exclude diabetes (e.g. impaired fasting glycaemia), an oral glucose tolerance test may be required. A dose of 1.75 g/kg (max. 75 g) of anhydrous glucose is used. It is also used to establish the presence of gestational diabetes; this generally involves giving anhydrous glucose 75 g (equivalent to Glucose BP 82.5 g) by mouth to the fasting patient, and measuring blood-glucose concentration at intervals. The appropriate amount of glucose should be given with 200–300 mL fluid. Alternatively anhydrous glucose 75 g can be given as 113 mL *Polycal®* with extra fluid to administer a total volume of 200–300 mL, or as *Rapilose®* OGTT oral solution.

6.2 Thyroid and antithyroid drugs**6.2.1 Thyroid hormones****6.2.2 Antithyroid drugs****6.2.1 Thyroid hormones**

Thyroid hormones are used in hypothyroidism (juvenile myxoedema), and also in diffuse non-toxic goitre, congenital or neonatal hypothyroidism, and Hashimoto's thyroiditis (lymphadenoid goitre). Neonatal hypothyroidism requires prompt treatment to facilitate normal development.

Levothyroxine sodium (thyroxine sodium) is the treatment of choice for *maintenance* therapy.

Doses for congenital hypothyroidism and juvenile myxoedema should be titrated according to clinical response, growth assessment, and measurement of plasma thyroxine and thyroid-stimulating hormone concentrations. In congenital hypothyroidism higher initial doses may normalise metabolism more quickly, with associated beneficial effects on mental development.

Liothyronine sodium has a similar action to levothyroxine but is more rapidly metabolised and has a more rapid effect; 20–25 micrograms is equivalent to approximately 100 micrograms of levothyroxine. Its effects develop after a few hours and disappear within 24 to 48 hours of discontinuing treatment. It may be used in *severe hypothyroid states* when a rapid response is desired.

Liothyronine by intravenous injection is the treatment of choice in *hypothyroid coma*. Adjunctive therapy includes intravenous fluids, hydrocortisone, and treatment of infection; assisted ventilation is often required.

LEVOTHYROXINE SODIUM
(Thyroxine sodium)

Cautions panhypopituitarism or predisposition to adrenal insufficiency (adrenal corticosteroid therapy before starting levothyroxine); cardiac disorders (monitor ECG; start at low dose and carefully titrate); long-standing hypothyroidism, diabetes insipidus, diabetes mellitus (dose of antidiabetic drugs including insulin may need to be increased); **interactions:** Appendix 1 (thyroid hormones)

Pregnancy monitor maternal serum-thyrotrophin concentration—levothyroxine may cross the placenta and excessive maternal concentration can be detrimental to fetus

Breast-feeding amount too small to affect tests for neonatal hypothyroidism

Side-effects usually at excessive dosage include diarrhoea, vomiting; anginal pain, arrhythmias, palpitation, tachycardia, benign intracranial hypertension; tremor, restlessness, excitability, insomnia, headache, flushing, sweating, fever, heat intolerance, weight loss, nervousness; craniosynostosis and premature closure of epiphyses; menstrual irregularities; eosinophilia, liver dysfunction; muscle cramps, muscular weakness; transient hair loss; hypersensitivity reactions including rash, pruritus and oedema also reported

Indications and dose

Levothyroxine equivalent to 100 micrograms/m²/day can be used as a guide to the requirements in children

Hypothyroidism● **By mouth**

Neonate initially 10–15 micrograms/kg once daily (max. 50 micrograms daily), adjusted in steps of 5 micrograms/kg every 2 weeks or as necessary; usual maintenance dose 20–50 micrograms daily

Child 1 month–2 years initially 5 micrograms/kg once daily (max. 50 micrograms daily) adjusted in steps of 10–25 micrograms daily every 2–4 weeks until metabolism normalised; usual maintenance dose 25–75 micrograms daily

Child 2–12 years initially 50 micrograms once daily adjusted in steps of 25 micrograms daily every 2–4 weeks until metabolism normalised; usual maintenance dose 75–100 micrograms daily

Child 12–18 years initially 50 micrograms once daily adjusted in steps of 25–50 micrograms daily every 3–4 weeks until metabolism normalised; usual maintenance dose 100–200 micrograms daily

Levothyroxine (Non-proprietary) (PoM)

Tablets, levothyroxine sodium 25 micrograms, net price 28-tab pack = £2.58; 50 micrograms, 28-tab pack = £1.76; 100 micrograms, 28-tab pack = £1.76

Brands include *Eltroxin*®

Oral solution, levothyroxine sodium 25 micrograms/5 mL, net price 100 mL = £54.24; 50 micrograms/5 mL, 100 mL = £60.97; 100 micrograms/5 mL, 100 mL = £88.53

LIOTHYRONINE SODIUM

(L-Tri-iodothyronine sodium)

Cautions severe and prolonged hypothyroidism (initiate corticosteroid therapy in adrenal insufficiency); cardiac disorders (monitor ECG; start at low dose and carefully titrate); diabetes insipidus, diabetes mellitus (dose of antidiabetic drugs including insulin may need to be increased); **interactions:** Appendix 1 (thyroid hormones)

Pregnancy does not cross the placenta in significant amounts; monitor maternal thyroid function tests—dosage adjustment may be necessary

Breast-feeding amount too small to affect tests for neonatal hypothyroidism

Side-effects usually at excessive dosage include diarrhoea; anginal pain, arrhythmias, palpitation, tachycardia; restlessness, excitability, headache, flushing, sweating, weight loss; muscle cramps, muscle weakness

Indications and dose

See also notes above

Hypothyroidism

• By mouth

Child 12–18 years initially 10–20 micrograms daily gradually increased to 60 micrograms daily in 2–3 divided doses

• By slow intravenous injection

(replacement for oral levothyroxine)

Convert **daily** levothyroxine dose to liothyronine (see notes above for approximate equivalence) and give in 2–3 divided doses, adjusted according to response

Hypothyroid coma

• By slow intravenous injection

Child 12–18 years 5–20 micrograms repeated every 12 hours or up to every 4 hours if necessary; *alternatively* initially 50 micrograms then 25 micrograms every 8 hours reducing to 25 micrograms twice daily

Liothyronine sodium (Non-proprietary) (PoM)

Tablets, scored, liothyronine sodium 20 micrograms, net price 28-tab pack = £102.30

Important patients switched to a different brand should be monitored (particularly if pregnant or if heart disease

present) as brands without a UK licence may not be bioequivalent and dose adjustment may be necessary; pregnant women or those with heart disease should undergo an early review of thyroid status, and other patients should have thyroid function assessed if experiencing a significant change in symptoms. If liothyronine is continued long-term, thyroid function tests should be repeated 1–2 months after any change in brand.

Injection, powder for reconstitution, liothyronine sodium, net price 20-microgram vial = £22.50

6.2.2 Antithyroid drugs

Antithyroid drugs are used for hyperthyroidism either to prepare children for thyroidectomy or for long-term management. In the UK **carbimazole** is the most commonly used drug. **Propylthiouracil** should be reserved for children who are intolerant of, or who experience sensitivity reactions to, carbimazole (sensitivity is not necessarily displayed to both drugs), and for whom other treatments are inappropriate. Both drugs act primarily by interfering with the synthesis of thyroid hormones.

Treatment in children should be undertaken by a specialist.

Neutropenia and agranulocytosis

Doctors are reminded of the importance of recognising bone marrow suppression induced by carbimazole and the need to stop treatment promptly.

1. Children and their carers should be asked to report symptoms and signs suggestive of infection, especially sore throat.
2. A white blood cell count should be performed if there is any clinical evidence of infection.
3. Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia.

Carbimazole or **propylthiouracil** are initially given in large doses to block thyroid function. This dose is continued until the child becomes euthyroid, usually after 4 to 8 weeks, and is then gradually reduced to a maintenance dose of 30–60% of the initial dose. Alternatively high-dose treatment is continued in combination with levothyroxine replacement (*blocking-replacement regimen*); this is particularly useful when dose adjustment proves difficult. Treatment is usually continued for 12 to 24 months. The blocking-replacement regimen is **not** suitable during pregnancy. Hypothyroidism should be avoided particularly during pregnancy as it can cause fetal goitre.

When substituting, carbimazole 1 mg is considered equivalent to propylthiouracil 10 mg but the dose may need adjusting according to response.

Rashes and pruritus are common with carbimazole but they can be treated with antihistamines without discontinuing therapy; alternatively propylthiouracil can be substituted. If a child on carbimazole develops a sore throat it should be reported immediately because of the rare complication of agranulocytosis (see Neutropenia and Agranulocytosis, above).

Iodine has been used as an adjunct to antithyroid drugs for 10 to 14 days before partial thyroidectomy; however, there is little evidence of a beneficial effect. Iodine should not be used for long-term treatment because its antithyroid action tends to diminish.

Radioactive sodium iodide (^{131}I) solution is used increasingly for the treatment of thyrotoxicosis at all ages, particularly where medical therapy or compliance is a problem, in patients with cardiac disease, and in patients who relapse after thyroidectomy.

Propranolol (section 2.4) is useful for rapid relief of thyrotoxic symptoms and can be used in conjunction with antithyroid drugs or as an adjunct to radioactive iodine. Beta-blockers are also useful in neonatal thyrotoxicosis and in supraventricular arrhythmias due to hyperthyroidism. Propranolol has been used in conjunction with iodine to prepare mildly thyrotoxic patients for surgery but it is preferable to make the patient euthyroid with carbimazole. Laboratory tests of thyroid function are not altered by beta-blockers. Most experience in treating thyrotoxicosis has been gained with propranolol but **atenolol** (section 2.4) is also used.

Thyrotoxic crisis ('thyroid storm') requires emergency treatment with intravenous administration of fluids, propranolol and hydrocortisone as sodium succinate, as well as oral iodine solution and carbimazole or propylthiouracil which may need to be administered by nasogastric tube.

Neonatal hyperthyroidism is treated with carbimazole or propylthiouracil, usually for 8 to 12 weeks. In severe symptomatic disease iodine may be needed to block the thyroid and propranolol required to treat peripheral symptoms.

Pregnancy Radioactive iodine therapy is contra-indicated during pregnancy. Propylthiouracil and carbimazole can be given but the blocking-replacement regimen (see above) is **not** suitable. Rarely, carbimazole has been associated with congenital defects, including aplasia cutis of the neonate, therefore propylthiouracil remains the drug of choice during the first trimester of pregnancy. In the second trimester, consider switching to carbimazole because of the potential risk of hepatotoxicity with propylthiouracil. Both propylthiouracil and carbimazole cross the placenta and in high doses can cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves' disease tend to fall during pregnancy).

Breast-feeding Carbimazole and propylthiouracil are present in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used.

CARBIMAZOLE

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe hepatic impairment

Pregnancy see notes above

Breast-feeding amount in milk may be sufficient to affect neonatal thyroid function, therefore lowest effective dose should be used; see notes above

Side-effects nausea, mild gastro-intestinal disturbances, taste disturbance, hepatic disorders (including hepatitis and jaundice), headache, fever, malaise, rash, pruritus, arthralgia; *rarely* myopathy, alopecia, bone marrow suppression (including pancytopenia and agranulocytosis, see Neutropenia and Agranulocytosis above), hypersensitivity reactions

Indications and dose

Hyperthyroidism (including Graves' disease)

• By mouth

Neonate initially 750 micrograms/kg daily in single or divided doses until euthyroid then adjust as necessary (see notes above); higher initial doses (up to 1 mg/kg daily) are occasionally required, particularly in thyrotoxic crisis

Child 1 month–12 years initially 750 micrograms/kg (max. 30 mg) daily in single or divided doses until euthyroid then adjusted as necessary (see notes above); higher initial doses occasionally required, particularly in thyrotoxic crisis

Child 12–18 years initially 30 mg daily in single or divided doses until euthyroid then adjusted as necessary (see notes above); higher initial doses occasionally required, particularly in thyrotoxic crisis

Counselling Warn child and carers to tell doctor **immediately** if sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness develops

Carbimazole (Non-proprietary) (PoM)

Tablets, carbimazole 5 mg, net price 100-tab pack = £46.50; 20 mg, 100-tab pack = £114.93. Counselling, blood disorder symptoms

IODINE AND IODIDE

Cautions not for long-term treatment

Pregnancy neonatal goitre and hypothyroidism; see also notes above

Breast-feeding stop breast-feeding; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk; see also notes above

Side-effects hypersensitivity reactions including cornea-like symptoms, headache, lacrimation, conjunctivitis, pain in salivary glands, laryngitis, bronchitis, rashes; on prolonged treatment depression, insomnia, impotence; goitre in infants of mothers taking iodides

Indications and dose

See under preparation

Aqueous Iodine Oral Solution

Oral solution, iodine 5%, potassium iodide 10% in purified water, freshly boiled and cooled, total iodine 130 mg/mL, net price 500 mL = £9.23. Label: 27 Dose

Neonatal thyrotoxicosis

• By mouth

Neonate 0.05–0.1 mL 3 times daily

Thyrotoxicosis (pre-operative)

• By mouth

Neonate 0.1–0.3 mL 3 times daily

Child 1 month–18 years 0.1–0.3 mL 3 times daily

Thyrotoxic crisis

• By mouth

Child 1 month–1 year 0.2–0.3 mL 3 times daily

Administration Dilute well with milk or water

PROPYLTHIOURACIL

Cautions monitor for hepatotoxicity

Hepatotoxicity Severe hepatic reactions have been reported, including fatal cases and cases requiring liver

transplant—discontinue if significant liver-enzyme abnormalities develop

Counselling Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, jaundice, dark urine, or pruritus develop

Hepatic impairment reduce dose (see also Hepatotoxicity above)

Renal impairment estimated glomerular filtration rate 10–50 mL/minute/1.73 m², use 75% of normal dose; estimated glomerular filtration rate less than 10 mL/minute/1.73 m², use 50% of normal dose

Pregnancy see notes above

Breast-feeding monitor infant's thyroid status but amount in milk probably too small to affect infant; high doses may affect neonatal thyroid function; see also notes above

Side-effects see under Carbimazole; leucopenia; rarely cutaneous vasculitis, thrombocytopenia, aplastic anaemia, hypoprothrombinaemia, hepatic disorders (including hepatitis, hepatic failure, encephalopathy, hepatic necrosis; see also Hepatotoxicity above), nephritis, lupus erythematosus-like syndromes

Licensed use not licensed for use in children under 6 years of age

Indications and dose

Hyperthyroidism (including Graves' disease)

• By mouth

Neonate initially 2.5–5 mg/kg twice daily until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis

Child 1 month–1 year initially 2.5 mg/kg 3 times daily until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis

Child 1–5 years initially 25 mg 3 times daily until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis

Child 5–12 years initially 50 mg 3 times daily until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis

Child 12–18 years initially 100 mg 3 times daily administered until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis

Propylthiouracil (Non-proprietary) (POM)

Tablets, propylthiouracil 50 mg, net price 56-tab pack = £59.93, 100-tab pack = £96.32

PROPRANOLOL HYDROCHLORIDE

Cautions see section 2.4

Contra-indications see section 2.4

Hepatic impairment section 2.4

Renal impairment section 2.4

Pregnancy section 2.4

Breast-feeding section 2.4

Side-effects see section 2.4

Indications and dose

Hyperthyroidism with autonomic symptoms, thyrotoxicosis, thyrotoxic crisis

• By mouth

Neonate initially 250–500 micrograms/kg every 6–8 hours, adjusted according to response

Child 1 month–18 years initially 250–500 micrograms/kg every 8 hours, then adjusted according to response; doses up to 1 mg/kg every 8 hours occasionally required, max. 40 mg every 8 hours

• By intravenous injection over 10 minutes

Neonate initially 20–50 micrograms/kg every 6–8 hours, adjusted according to response

Child 1 month–18 years initially 25–50 micrograms/kg (max. 5 mg) every 6–8 hours, adjusted according to response

Preparations

See section 2.4

6.3 Corticosteroids

6.3.1 Replacement therapy

6.3.2 Glucocorticoid therapy

6.3.1 Replacement therapy

The adrenal cortex normally secretes hydrocortisone (cortisol) which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone.

In deficiency states, physiological replacement is best achieved with a combination of **hydrocortisone** (section 6.3.2) and the mineralocorticoid **fludrocortisone**; hydrocortisone alone does not usually provide sufficient mineralocorticoid activity for complete replacement.

In *Addison's disease* or following adrenalectomy, **hydrocortisone** by mouth is usually required. This is given in 2–3 divided doses, the larger in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion. The optimum daily dose is determined on the basis of clinical response. Glucocorticoid therapy is supplemented by fludrocortisone.

In *acute adrenocortical insufficiency*, **hydrocortisone** is given intravenously (preferably as sodium succinate) every 6 to 8 hours in sodium chloride intravenous infusion 0.9%.

In *hypopituitarism*, glucocorticoids should be given as in adrenocortical insufficiency, but since production of aldosterone is also regulated by the renin-angiotensin system a mineralocorticoid is not usually required. Additional replacement therapy with levothyroxine (section 6.2.1) and sex hormones (section 6.4) should be given as indicated by the pattern of hormone deficiency.

In *congenital adrenal hyperplasia*, the pituitary gland increases production of corticotropin to compensate for reduced formation of cortisol; this results in excessive adrenal androgen production. Treatment is aimed at suppressing corticotropin using hydrocortisone (section 6.3.2). Careful and continual dose titration is required to avoid growth retardation and toxicity; for this reason potent, synthetic glucocorticoids such as dexamethasone are usually reserved for in adolescents. The dose is adjusted according to clinical

response and measurement of adrenal androgens and 17-hydroxyprogesterone. Salt-losing forms of congenital adrenal hyperplasia (where there is a lack of aldosterone production) also require mineralocorticoid replacement and salt supplementation (particularly in early life). The dose of mineralocorticoid is adjusted according to electrolyte concentration and plasma-renin activity.

FLUDROCORTISONE ACETATE

Cautions section 6.3.2; **interactions:** Appendix 1 (corticosteroids)

Contra-indications section 6.3.2

Hepatic impairment see section 6.3.2

Renal impairment see section 6.3.2

Pregnancy see section 6.3.2

Breast-feeding see section 6.3.2

Side-effects section 6.3.2

Indications and dose

Mineralocorticoid replacement in adrenocortical insufficiency

• By mouth

Neonate initially 50 micrograms once daily, adjusted according to response; usual range 50–200 micrograms daily; higher doses may be required

Child 1 month–18 years initially 50–100 micrograms once daily; maintenance 50–300 micrograms once daily, adjusted according to response

Note Dose adjustment may be required if salt supplements are administered

Florinef® (Squibb) (PoM)

Tablets, scored, fludrocortisone acetate 100 micrograms. Net price 100-tab pack = £5.05. Label: 10, steroid card

6.3.2 Glucocorticoid therapy

In comparing the relative potencies of corticosteroids in terms of their anti-inflammatory (glucocorticoid) effects it should be borne in mind that high glucocorticoid activity in itself is of no advantage unless it is accompanied by relatively low mineralocorticoid activity (see Disadvantages of Corticosteroids below). The mineralocorticoid activity of **fludrocortisone** (section 6.3.1) is so high that its anti-inflammatory activity is of no clinical relevance. The table below shows equivalent anti-inflammatory doses.

Equivalent anti-inflammatory doses of corticosteroids

This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action

Prednisolone 1 mg	≡	Betamethasone 150 micrograms
	≡	Deflazacort 1.2 mg
	≡	Dexamethasone 150 micrograms
	≡	Hydrocortisone 4 mg
	≡	Methylprednisolone 800 micrograms
	≡	Triamcinolone 800 micrograms

The relatively high mineralocorticoid activity of **hydrocortisone**, and the resulting fluid retention, makes it unsuitable for disease suppression on a long-term basis. However, hydrocortisone can be used for adrenal replacement therapy (section 6.3.1). Hydrocortisone is used on a short-term basis by intravenous injection for the emergency management of some conditions. The relatively moderate anti-inflammatory potency of hydrocortisone also makes it a useful topical corticosteroid for the management of inflammatory skin conditions because side-effects (both topical and systemic) are less marked (section 13.4).

Prednisolone has predominantly glucocorticoid activity and is the corticosteroid most commonly used by mouth for long-term disease suppression.

Betamethasone and **dexamethasone** have very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity. This makes them particularly suitable for high-dose therapy in conditions where fluid retention would be a disadvantage.

Betamethasone and dexamethasone also have a long duration of action and this, coupled with their lack of mineralocorticoid action makes them particularly suitable for conditions which require suppression of corticotropin (corticotrophin) secretion. Some esters of betamethasone and of **beclo-methasone** (beclo-methasone) exert a considerably more marked topical effect (e.g. on the skin or the lungs) than when given by mouth; use is made of this to obtain topical effects whilst minimising systemic side-effects (e.g. for skin applications and asthma inhalations).

Deflazacort has a high glucocorticoid activity; it is derived from prednisolone.

Use of corticosteroids

Dosages of corticosteroids vary widely in different diseases and in different children. If the use of a corticosteroid can save or prolong life, as in exfoliative dermatitis, pemphigus, acute leukaemia or acute transplant rejection, high doses may need to be given, because the complications of therapy are likely to be less serious than the effects of the disease itself.

When long-term corticosteroid therapy is used in some chronic diseases, the adverse effects of treatment may become greater than the disabilities caused by the disease. To minimise side-effects the maintenance dose should be kept as low as possible.

When potentially less harmful measures are ineffective corticosteroids are used topically for the treatment of inflammatory conditions of the skin (section 13.4). Corticosteroids should be avoided or used only under specialist supervision in psoriasis (section 13.5).

Corticosteroids are used both topically (by rectum) and systemically (by mouth or intravenously) in the management of ulcerative colitis and Crohn's disease (section 1.5 and section 1.7.2).

Use can be made of the mineralocorticoid activity of fludrocortisone to treat postural hypotension in autonomic neuropathy.

High-dose corticosteroids should be avoided for the management of septic shock. However, low-dose hydrocortisone can be used in septic shock (section 2.7.1) that is resistant to volume expansion and catecholamines, and is accompanied by suspected or proven adrenal insufficiency.

The suppressive action of glucocorticoids on the hypothalamic-pituitary-adrenal axis is greatest and most prolonged when they are given at night. In most adults a single dose of 1 mg of dexamethasone at night is sufficient to inhibit corticotropin secretion for 24 hours. This is the basis of the 'overnight dexamethasone suppression test' for diagnosing Cushing's syndrome.

Betamethasone and dexamethasone are also appropriate for conditions where water retention would be a disadvantage.

A corticosteroid can be used in the management of raised intracranial pressure or cerebral oedema that occurs as a result of malignancy (see also p. 18); high doses of betamethasone or dexamethasone are generally used. However, a corticosteroid should **not** be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.

In acute hypersensitivity reactions, such as angioedema of the upper respiratory tract and anaphylaxis, corticosteroids are indicated as an adjunct to emergency treatment with adrenaline (epinephrine) (section 3.4.3). In such cases hydrocortisone (as sodium succinate) by intravenous injection may be required.

In the management of asthma, corticosteroids are preferably used by inhalation (section 3.2) but systemic therapy along with bronchodilators is required for the emergency treatment of severe acute asthma (section 3.1.1).

Betamethasone is used in women at risk of preterm delivery to reduce the incidence of neonatal respiratory distress syndrome [unlicensed use].

Dexamethasone should not be used routinely for the prophylaxis and treatment of chronic lung disease in neonates because of an association with adverse neurological effects.

Corticosteroids may be useful in conditions such as auto-immune hepatitis, rheumatoid arthritis, and sarcoidosis; they may also lead to remissions of acquired haemolytic anaemia (section 9.1.3) and thrombocytopenic purpura (section 9.1.4).

High doses of a corticosteroid (usually prednisolone) are used in the treatment of *glomerular kidney disease*, including *nephrotic syndrome*. The condition frequently recurs; a corticosteroid given in high doses and for prolonged periods may delay relapse but the higher incidence of adverse effects limits the overall benefit. Those who suffer frequent relapses may be treated with prednisolone given in a low dose (daily or on alternate days) for 3–6 months; the dose should be adjusted to minimise effects on growth and development. Other drugs used in the treatment of glomerular kidney disease include levamisole (section 5.5.2), cyclophosphamide and chlorambucil (section 8.1.1), and ciclosporin (section 8.2.2). *Congenital nephrotic syndrome* may be resistant to corticosteroids and immunosuppressants; indometacin (section 10.1.1) and an ACE inhibitor such as captopril (section 2.5.5.1) have been used.

Corticosteroids can improve the prognosis of serious conditions such as systemic lupus erythematosus and polyarteritis nodosa; the effects of the disease process may be suppressed and symptoms relieved, but the underlying condition is not cured, although it may ultimately remit. It is usual to begin therapy in these conditions at fairly high dose and then to reduce the dose to the lowest commensurate with disease control.

For other references to the use of corticosteroids see Prescribing in Palliative Care (p. 17), section 8.2.2 (immunosuppression), section 10.1.2 (rheumatic diseases), section 11.4 (eye), section 12.1.1 (otitis externa), section 12.2.1 (allergic rhinitis), and section 12.3.1 (aphthous ulcers).

Administration

Whenever possible *local treatment* with creams, intra-articular injections, inhalations, eye-drops, or enemas should be used in preference to *systemic treatment*. The suppressive action of a corticosteroid on cortisol secretion is least when it is given as a single dose in the morning. In an attempt to reduce pituitary-adrenal suppression further, the total dose for two days can sometimes be taken as a single dose on alternate days; alternate-day administration has not been very successful in the management of asthma (section 3.2). Pituitary-adrenal suppression can also be reduced by means of intermittent therapy with short courses. In some conditions it may be possible to reduce the dose of corticosteroid by adding a small dose of an immunosuppressive drug (section 8.2.1).

Cautions and contra-indications of corticosteroids

Adrenal suppression

During prolonged therapy with corticosteroids, adrenal atrophy develops and can persist for years after stopping. Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension, or death (see Withdrawal of Corticosteroids, below). Withdrawal can also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules, and weight loss.

To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgical procedure requires a temporary increase in corticosteroid dose, or if already stopped, a temporary re-introduction of corticosteroid treatment. To avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period, anaesthetists **must** know whether a patient is taking or has been taking a corticosteroid. A regimen for corticosteroid replacement may be necessary before and after surgery.

Children on long-term corticosteroid treatment should carry a Steroid Treatment Card (see p. 379) which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment.

Infections

Prolonged courses of corticosteroids increase susceptibility to infections and severity of infections; clinical presentation of infections may also be atypical. Serious infections, e.g. *septicaemia* and *tuberculosis*, may reach an advanced stage before being recognised, and *amoebiasis* or *strongyloidiasis* may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral *ocular infections* may also be exacerbated (see also section 11.4.1).

Chickenpox Unless they have had chickenpox, children receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded

as being *at risk of severe chickenpox* (see Steroid Treatment Card). Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature.

Passive immunisation with varicella–zoster immunoglobulin (section 14.5.2) is needed for exposed non-immune children receiving systemic corticosteroids or for those who have used them within the previous 3 months. Confirmed chickenpox warrants specialist care and urgent treatment (section 5.3.2.1). Corticosteroids should not be stopped and dosage may need to be increased.

Topical, inhaled or rectal corticosteroids are less likely to be associated with an increased risk of severe chickenpox.

Measles Children taking corticosteroids, and their carers, should be advised to take particular care to avoid exposure to measles and to seek urgent medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin (section 14.5.1) may be needed.

Withdrawal of corticosteroids

The magnitude and speed of dose reduction in corticosteroid withdrawal should be determined on a case-by-case basis, taking into consideration the underlying condition that is being treated, and individual patient factors such as the likelihood of relapse and the duration of corticosteroid treatment. *Gradual* withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:

- received more than 40 mg prednisolone (or equivalent) daily for more than 1 week or 2 mg/kg daily for 1 week or 1 mg/kg daily for 1 month;
- been given repeat doses in the evening;
- received more than 3 weeks' treatment;
- recently received repeated courses (particularly if taken for longer than 3 weeks);
- taken a short course within 1 year of stopping long-term therapy;
- other possible causes of adrenal suppression.

Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse *and* who have received treatment for 3 weeks or less *and* who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to prednisolone 2–2.5 mg/m² daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

Psychiatric reactions

Systemic corticosteroids, particularly in high doses, are linked to psychiatric reactions including euphoria, nightmares, insomnia, irritability, mood lability, suicidal thoughts, psychotic reactions, and behavioural disturbances. A serious paranoid state or depression with risk of suicide can be induced, particularly in children with a history of mental disorder. These reactions frequently subside on reducing the dose or discontinuing the corticosteroid but they may also require specific management. Children and their carers should be advised to seek medical advice if psychiatric symptoms (especially depression and suicidal thoughts) occur and they should also be alert to the rare possibility of such reactions during withdrawal of corticosteroid treatment.

Systemic corticosteroids should be prescribed with care in those predisposed to psychiatric reactions, including those who have previously suffered corticosteroid-induced psychosis, or who have a personal or family history of psychiatric disorders.

Advice to children and carers

A patient information leaflet should be supplied to every patient when a systemic corticosteroid is prescribed. Children and carers should especially be advised of the following (for details, see Infections, Adrenal Suppression, and Psychiatric Reactions above and Withdrawal of Corticosteroids below):

- **Immunosuppression** Prolonged courses of corticosteroids can increase susceptibility to infection and serious infections can go unrecognised. Unless already immune, children are at risk of severe **chickenpox** and should avoid close contact with people who have chickenpox or shingles. Similarly, precautions should also be taken against contracting **measles**;
- **Adrenal suppression** If the corticosteroid is given for longer than 3 weeks, treatment must not be stopped abruptly. Adrenal suppression can last for a year or more after stopping treatment and the child or carer must mention the course of corticosteroid when receiving treatment for any illness or injury;
- **Mood and behaviour changes** Corticosteroid treatment, especially with high doses, can alter mood and behaviour early in treatment—the child can become confused, irritable and suffer from delusion and suicidal thoughts. These effects can also occur when corticosteroid treatment is being withdrawn. Medical advice should be sought if worrying psychological changes occur;
- **Other serious effects** Serious gastro-intestinal, musculoskeletal, and ophthalmic effects which require medical help can also occur; for details see Side-effects of Corticosteroids, p. 379.

Steroid treatment cards

Steroid treatment cards (see p. 379) should be issued where appropriate, and are available for purchase from:

3M Security Print and Systems Limited
Gorse Street, Chadderton
Oldham., OL9 9QH
Tel: 0845 610 1112

GP practices can obtain supplies through their Local Area Team Stores. NHS Trusts can order supplies from www.nhsforms.co.uk or by emailing nhsforms@mmm.com.

Other cautions and contra-indications

Other cautions include: growth restriction—possibly irreversible, frequent monitoring required if history of tuberculosis (or X-ray changes), hypertension, congestive heart failure, diabetes mellitus including family history, osteoporosis, susceptibility to angle-closure glaucoma (including family history), ocular herpes simplex—risk of corneal perforation, severe affective disorders (particularly if history of steroid-induced psychosis—see also Psychiatric Reactions above), epilepsy, peptic ulcer, hypothyroidism, history of steroid myopathy, ulcerative colitis, diverticulitis, recent intestinal anastomoses, thromboembolic disorders, myasthenia gravis; **interactions:** Appendix 1 (corticosteroids)

Other contra-indications include: systemic infection (unless specific therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished)

STEROID TREATMENT CARD

I am a patient on STEROID treatment which must not be stopped suddenly

- If you have been taking this medicine for more than three weeks, the dose should be reduced gradually when you stop taking steroids unless your doctor says otherwise.
- Read the patient information leaflet given with the medicine.
- Always carry this card with you and show it to anyone who treats you (for example a doctor, nurse, pharmacist or dentist). For one year after you stop the treatment, you must mention that you have taken steroids.
- If you become ill, or if you come into contact with anyone who has an infectious disease, consult your doctor promptly. If you have never had chickenpox, you should avoid close contact with people who have chickenpox or shingles. If you do come into contact with chickenpox, see your doctor urgently.
- Make sure that the information on the card is kept up to date.

Hepatic impairment

When corticosteroids are administered orally or parenterally, the plasma-drug concentration may be increased in children with hepatic impairment. Corticosteroids should be used with caution in hepatic impairment and the child should be monitored closely.

Renal impairment

Oral and parenteral preparations of corticosteroids should be used with caution in children with renal impairment.

Pregnancy and breast-feeding

The benefit of treatment with corticosteroids during pregnancy and breast-feeding outweighs the risk; pregnant women with fluid retention should be monitored closely. Corticosteroid cover will be required during labour.

Following a review of the data on the safety of systemic corticosteroids used in pregnancy and breast-feeding the CSM (May 1998) concluded:

- corticosteroids vary in their ability to cross the placenta; betamethasone and dexamethasone cross the placenta readily while 88% of prednisolone is inactivated as it crosses the placenta;

- there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities such as cleft palate or lip;
- when administration is prolonged or repeated during pregnancy, systemic corticosteroids increase the risk of intra-uterine growth restriction; there is no evidence of intra-uterine growth restriction following short-term treatment (e.g. prophylactic treatment for neonatal respiratory distress syndrome);
- any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important;
- prednisolone appears in small amounts in breast milk but maternal doses of up to 40 mg daily are unlikely to cause systemic effects in the infant; infants should be monitored for adrenal suppression if the mothers are taking a higher dose.

Side-effects of corticosteroids

Overdosage or prolonged use can exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid side-effects.

Corticosteroids suppress growth and can affect the development of puberty. It is important to use the lowest effective dose; alternate-day regimens may be appropriate and limit growth reduction. For the effect of corticosteroids given in pregnancy, see Pregnancy and Breast-feeding, p. 379.

Mineralocorticoid side-effects include hypertension, sodium and water retention, and potassium, and calcium loss. They are most marked with fludrocortisone, but are significant with hydrocortisone, corticotropin, and tetracosactide. Mineralocorticoid actions are negligible with the high potency glucocorticoids, betamethasone and dexamethasone, and occur only slightly with methylprednisolone, prednisolone, and triamcinolone.

Glucocorticoid side-effects include diabetes and osteoporosis (section 6.6); in addition high doses are associated with avascular necrosis of the femoral head. Muscle wasting (proximal myopathy) can also occur. Corticosteroid therapy is also weakly linked with peptic ulceration; there is no conclusive evidence that the use of enteric-coated preparations of prednisolone reduces the risk of peptic ulceration. See also Psychiatric Reactions, p. 378.

High doses of corticosteroids can cause Cushing's syndrome, with moon face, striae, and acne; it is usually reversible on withdrawal of treatment, but this must always be gradually tapered to avoid symptoms of acute adrenal insufficiency (**important**: see also Adrenal Suppression, p. 377).

Side-effects can be minimised by using the lowest effective dose for the minimum period possible.

Other side effects include: **gastro-intestinal effects:** dyspepsia, abdominal distension, acute pancreatitis, oesophageal ulceration and candidiasis; **musculoskeletal effects:** muscle weakness, vertebral and long bone fractures, tendon rupture; **endocrine effects:** menstrual irregularities and amenorrhoea, hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite; increased susceptibility to and severity of infection, reactivation of dormant tuberculosis; **neuropsychiatric effects:** psychological dependence, insomnia, increased intracranial pressure with papilloedema (usually after

withdrawal), aggravation of schizophrenia, aggravation of epilepsy; *ophthalmic effects*: papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease, increased intra-ocular pressure, exophthalmos, *very rarely* angle-closure glaucoma; *also* impaired healing, petechiae, ecchymoses, facial erythema, suppression of skin test reactions, urticaria, hyperhidrosis, skin atrophy, bruising, telangiectasia, myocardial rupture following recent myocardial infarction, congestive heart failure, leucocytosis, hyperglycaemia, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise, hiccups, headache, vertigo.

For other references to the side-effects of corticosteroids see section 1.5 (gastro-intestinal system), section 3.2 (asthma), section 11.4 (eye) and section 13.4 (skin).

BETAMETHASONE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above; transient effect on fetal movements and heart rate

Breast-feeding see notes above

Side-effects see notes above

Licensed use *Betnesol*[®] tablets not licensed for use as mouthwash

Indications and dose

Suppression of inflammatory and allergic disorders; congenital adrenal hyperplasia; *see also notes above*

- By slow intravenous injection or by intravenous infusion

Child 1 month–1 year initially 1 mg repeated up to 4 times in 24 hours according to response

Child 1–6 years initially 2 mg repeated up to 4 times in 24 hours according to response

Child 6–12 years initially 4 mg repeated up to 4 times in 24 hours according to response

Child 12–18 years initially 4–20 mg repeated up to 4 times in 24 hours according to response

Eye section 11.4.1

Ear section 12.1.1

Nose section 12.2.1

Mouth section 12.3.1

Administration For *intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%

Betnesol[®] (RPH) *[PoM]*

Injection, betamethasone 4 mg (as sodium phosphate) /mL. Net price 1-mL amp = £1.22. Label: 10, steroid card

DEFLAZACORT

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

Inflammatory and allergic disorders

- By mouth

Child 1 month–12 years 0.25–1.5 mg/kg once daily or on alternate days; up to 2.4 mg/kg (max. 120 mg) daily has been used in emergency situations

Child 12–18 years 3–18 mg once daily or on alternate days; up to 2.4 mg/kg (max. 120 mg) daily has been used in emergency situations

Nephrotic syndrome

- By mouth

Child 1 month–18 years initially 1.5 mg/kg once daily (max. 120 mg) reduced to lowest effective dose for maintenance

Calcraft[®] (Sanofi-Aventis) *[PoM]*

Tablets, deflazacort 6 mg, net price 60-tab pack = £15.82. Label: 5, 10, steroid card

DEXAMETHASONE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also perineal irritation may follow intravenous administration of the phosphate ester

Licensed use consult product literature; not licensed for use in bacterial meningitis

Indications and dose

Inflammatory and allergic disorders

- By mouth

Child 1 month–18 years 10–100 micrograms/kg daily in 1–2 divided doses, adjusted according to response; up to 300 micrograms/kg daily may be required in emergency situations

- By intramuscular injection or slow intravenous injection or infusion

Child 1 month–12 years 83–333 micrograms/kg daily in 1–2 divided doses; max. 20 mg daily

Child 12–18 years initially 0.4–20 mg daily

Life-threatening cerebral oedema

- By intravenous injection

Child under 35 kg body-weight initially 16.7 mg, then 3.3 mg every 3 hours for 3 days, then 3.3 mg every 6 hours for 1 day, then 1.7 mg every 6 hours for 4 days, then decrease by 0.8 mg daily

Child over 35 kg body-weight initially 20.8 mg, then 3.3 mg every 2 hours for 3 days, then 3.3 mg every 4 hours for 1 day, then 3.3 mg every 6 hours for 4 days, then decrease by 1.7 mg daily

Bacterial meningitis (see section 5.1)

- By slow intravenous injection

Child 3 months–18 years 150 micrograms/kg (max. 10 mg) every 6 hours for 4 days starting before or with first dose of antibacterial

Physiological replacement

- By mouth or by slow intravenous injection

Child 1 month–18 years 250–500 micrograms/m² every 12 hours, adjusted according to response

Croup section 3.1

Nausea and vomiting with chemotherapy section 8.1

Rheumatic disease section 10.1.2

Eye section 11.4.1

Administration for administration *by mouth* tablets may be dispersed in water or injection solution given by mouth

For *intravenous infusion* dilute with Glucose 5% or Sodium Chloride 0.9%; give over 15–20 minutes

Dexamethasone (Non-proprietary) ^(PoM)

Tablets, dexamethasone 500 micrograms, net price 28-tab pack = £48.00; 2 mg, 50-tab pack = £7.06, 100-tab pack = £12.05. Label: 10, steroid card, 21

Oral solution, sugar-free, dexamethasone (as sodium phosphate) 2 mg/5 mL, net price 75-mL = £32.50, 150-mL = £42.30. Label: 10, steroid card, 21

Brands include *Dexsol*[®], *Martapan*[®]

Injection, dexamethasone (as sodium phosphate) 3.3 mg/mL, net price 1-mL amp = £1.14. Label: 10, steroid card

Injection, dexamethasone (as sodium phosphate) 4 mg/mL, net price 1-mL amp = 91p, 2-mL vial = £1.27. Label: 10, steroid card

HYDROCORTISONE

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also phosphate ester associated with paraesthesia and pain (particularly in the perineal region)

Indications and dose

Congenital adrenal hyperplasia see also section 6.3.1

- By mouth

Neonate 9–15 mg/m² in 3 divided doses, adjusted according to response

Child 1 month–18 years 9–15 mg/m² in 3 divided doses, adjusted according to response

Acute adrenocortical insufficiency (Addisonian crisis) see also notes above and section 6.3.1

- By slow intravenous administration

Neonate initially 10 mg *by slow intravenous injection* then 100 mg/m² daily *by continuous intravenous infusion* or in divided doses every 6–8 hours; adjusted according to response; when stable reduce over 4–5 days to oral maintenance dose

Child 1 month–12 years initially 2–4 mg/kg *by slow intravenous injection* or *infusion* then 2–4 mg/kg every 6 hours; adjusted according to response; when stable reduce over 4–5 days to oral maintenance dose

Child 12–18 years 100 mg every 6 to 8 hours *by slow intravenous injection* or *infusion*

Adrenal hypoplasia, Addison's disease, chronic maintenance or replacement therapy

- By mouth

Neonate 8–10 mg/m² daily in 3 divided doses; higher doses may be needed

Child 1 month–18 years 8–10 mg/m² daily in 3 divided doses; higher doses may be needed

Note Give larger doses in the morning and smaller doses in the evening

Inflammatory bowel disease—induction of remission see also section 1.5.2

- By intravenous injection

Child 2–18 years 2.5 mg/kg (max. 100 mg) every 6 hours

- By continuous intravenous infusion

Child 2–18 years 10 mg/kg daily (max. 400 mg daily)

Acute hypersensitivity reactions, angioedema see also section 3.4.3

- By intramuscular or intravenous injection

Child under 6 months initially 25 mg 3 times daily, adjusted according to response

Child 6 months–6 years initially 50 mg 3 times daily, adjusted according to response

Child 6–12 years initially 100 mg 3 times daily, adjusted according to response

Child 12–18 years initially 200 mg 3 times daily, adjusted according to response

Hypotension resistant to inotropic treatment and volume replacement (limited evidence)

- By intravenous injection

Neonate initially 2.5 mg/kg repeated if necessary after 4 hours, then 2.5 mg/kg every 6 hours for 48 hours or until blood pressure recovers, then dose reduced gradually over at least 48 hours

Child 1 month–18 years 1 mg/kg (max. 100 mg) every 6 hours

Severe acute asthma p. 132

Haemorrhoids section 1.7.2

Rheumatic disease section 10.1.2

Shock section 2.7.1

Skin section 13.4

Administration for *intravenous administration*, dilute with Glucose 5% or Sodium Chloride 0.9%; for *intermittent infusion* give over 20–30 minutes.

For administration *by mouth*, injection solution may be swallowed [unlicensed use] but consider phosphate content; alternatively *Corlan*[®] pellets (section 12.3.1) may be swallowed [unlicensed use]—pellets should not be cut as may not provide appropriate dose

Hydrocortisone (Non-proprietary) ^(PoM)

Tablets, scored, hydrocortisone 10 mg, net price 30-tab pack = £59.24; 20 mg, 30-tab pack = £65.04. Label: 10, steroid card, 21

¹Efcortisol® (AMCo) 

Injection, hydrocortisone 100 mg (as sodium phosphate)/mL, net price 1-mL amp = £1.08, 5-mL amp = £4.89. Label: 10, steroid card

Note Paraesthesia and pain (particularly in the perineal region) may follow intravenous injection of the phosphate ester

¹Solu-Cortef® (Pharmacia) 

Injection, powder for reconstitution, hydrocortisone (as sodium succinate). Net price 100-mg vial = 92p, 100-mg vial with 2-mL amp water for injections = £1.16. Label: 10, steroid card

METHYLPREDNISOLONE

Cautions see notes above; rapid intravenous administration of large doses associated with cardiovascular collapse

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

Inflammatory and allergic disorders

- By mouth, slow intravenous injection or by intravenous infusion

Child 1 month–18 years 0.5–1.7 mg/kg daily in 2–4 divided doses depending on condition and response

Treatment of graft rejection reactions

- By intravenous injection

Child 1 month–18 years 10–20 mg/kg or 400–600 mg/m² (max. 1 g) once daily for 3 days

Severe erythema multiforme, lupus nephritis, systemic onset juvenile idiopathic arthritis

- By intravenous injection

Child 1 month–18 years 10–30 mg/kg (max. 1 g) once daily or on alternate days for up to 3 doses

Immunosuppression section 8.2.2

Rheumatic disease section 10.1.2

Skin section 13.4

Administration intravenous injection given over 30 minutes; for intravenous infusion may be diluted with sodium chloride intravenous infusion 0.9% or 0.45%, or glucose intravenous infusion 5% or 10%

Medrone® (Pfizer) 

Tablets, scored, methylprednisolone 2 mg (pink), net price 30-tab pack = £3.88; 4 mg, 30-tab pack = £6.19; 16 mg, 30-tab pack = £17.17; 100 mg (blue), 20-tab pack = £48.32. Label: 10, steroid card, 21

Solu-Medrone® (Pharmacia) 

Injection, powder for reconstitution, methylprednisolone (as sodium succinate) (all with solvent). Net price 40-mg vial = £1.58; 125-mg vial = £4.75; 500-mg vial = £9.60; 1-g vial = £17.30; 2-g vial = £32.86. Label: 10, steroid card

Intramuscular depot**Depo-Medrone®** (Pharmacia) 

Injection (aqueous suspension), methylprednisolone acetate 40 mg/mL. Net price 1-mL vial = £3.44; 2-mL vial = £6.18; 3-mL vial = £8.96. Label: 10, steroid card

Dose

- By deep intramuscular injection into gluteal muscle seek specialist advice

PREDNISOLONE

Cautions see notes above; also Duchenne's muscular dystrophy (possible transient rhabdomyolysis and myoglobinuria following strenuous physical activity)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

Autoimmune inflammatory disorders (including juvenile idiopathic arthritis, connective tissue disorders and systemic lupus erythematosus)

- By mouth

Child 1 month–18 years initially 1–2 mg/kg once daily (usual max. 60 mg daily), then reduced after a few days if appropriate

Autoimmune hepatitis

- By mouth

Child 1 month–18 years initially 2 mg/kg once daily (max. 40 mg daily) then reduced to minimum effective dose

Corticosteroid replacement therapy

- By mouth

Child 12–18 years 2–2.5 mg/m² daily in 1–2 divided doses adjusted according to response

Infantile spasms

- By mouth

Child 1 month–2 years initially 10 mg 4 times daily for 14 days (if seizures not controlled after 7 days increase to 20 mg 3 times daily for 7 days); reduce dose gradually over 15 days until stopped (patients taking 40 mg daily, reduce dose in steps of 10 mg every 5 days, then stop; patients taking 60 mg daily, reduce dose to 40 mg daily for 5 days, then 20 mg daily for 5 days, then 10 mg daily for 5 days, then stop)

Idiopathic thrombocytopenic purpura

- By mouth

Child 1–10 years 1–2 mg/kg daily for max. 14 days or 4 mg/kg daily for max. 4 days

Nephrotic syndrome

- By mouth

Child 1 month–18 years initially 60 mg/m² once daily (max. 80 mg daily) for 4–6 weeks until proteinuria ceases then 40 mg/m² on alternate days for 4–6 weeks, then withdraw by reducing dose gradually; prevention of relapse 0.5–1 mg/kg once daily or on alternate days for 3–6 months

1.  restriction does not apply where administration is for saving life in emergency

Asthma see p. 144

Ear section 12.1.1

Eye section 11.4.1

Immunosuppression section 8.2.2

Inflammatory bowel disease section 1.5.2

Pneumocystis pneumonia section 5.4.8

Rheumatic disease section 10.1.2

Prednisolone (Non-proprietary) [PoM]

Tablets, prednisolone 1 mg, net price 28-tab pack = £1.03; 5 mg, 28-tab pack = £1.31; 25 mg, 56-tab pack = £40.00. Label: 10, steroid card, 21

Tablets, both e/c, prednisolone 2.5 mg, net price 28-tab pack = £1.86, 100-tab pack = £13.43; 5 mg, 28-tab pack = £1.89, 100-tab pack = £13.54. Label: 5, 10, steroid card, 25

Brands include *Deltacortril*®

Soluble tablets, prednisolone 5 mg (as sodium phosphate), net price 30-tab pack = £42.78. Label: 10, steroid card, 13, 21

6.4 Sex hormones

6.4.1 Female sex hormones

6.4.2 Male sex hormones and antagonists

6.4.3 Anabolic steroids

Sex hormone replacement therapy is indicated in children for the treatment of gonadotrophin deficiency, gonadal disorders, or delayed puberty that interferes with quality of life. Indications include constitutional delay in puberty, congenital or acquired hypogonadotrophic hypogonadism, hypergonadotrophic hypogonadism (Turner's syndrome, Klinefelter's syndrome), endocrine disorders (Cushing's syndrome or hyperprolactinaemia), and chronic illnesses, such as cystic fibrosis or sickle-cell disease, that may affect the onset of puberty.

Replacement therapy is generally started at the appropriate age for the development of puberty and should be managed by a paediatric endocrinologist. Patients with constitutional delay, chronic illness, or eating disorders may need only small doses of hormone supplements for 4 to 6 months to induce puberty and endogenous sex hormone production, which is then sustained. Patients with organic causes of hormone deficiency will require life-long replacement, adjusted to allow normal development.

Inadequate treatment may lead to poor bone mineralisation, resulting in fractures and osteoporosis.

6.4.1 Female sex hormones

6.4.1.1 Oestrogens

6.4.1.2 Progestogens

6.4.1.1 Oestrogens

Oestrogens are necessary for the development of female secondary sexual characteristics. If onset of puberty is delayed because of organic pathology, puberty can be

induced with ethinylestradiol in increasing doses, guided by breast staging and uterine scans. Cyclical progestogen replacement is added after 12–18 months of oestrogen treatment (see section 6.4.1.2). Once the adult dosage of oestrogen has been reached (20 micrograms ethinylestradiol daily), it may be more convenient to provide replacement either as a low-dose oestrogen containing oral contraceptive formulation [unlicensed indication] (see section 7.3.1) or as a combined oestrogen and progestogen hormone replacement therapy preparation [unlicensed indication] (see BNFC section 6.4.1.1). There is limited experience in the use of transdermal patches or gels in children; compliance and skin irritation are sometimes a problem.

Ethinylestradiol is occasionally used, under **specialist supervision**, for the management of hereditary haemorrhagic telangiectasia (but evidence of benefit is limited), for the prevention of tall stature, and in tests of growth hormone secretion (see below). Side-effects include nausea and fluid retention.

Topical oestrogen creams are used in the treatment of labial adhesions (see section 7.2.1)

ETHINYLESTRADIOL

(Ethinylestradiol)

Cautions see Combined Hormonal Contraceptives (section 7.3.1); **interactions**: Appendix 1 (Oestrogens)

Contra-indications cardiovascular disease (sodium retention with oedema), personal or family history of thromboembolism, acute porphyria; see also Combined Hormonal Contraceptives (section 7.3.1)

Hepatic impairment avoid in liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and jaundice

Pregnancy avoid

Breast-feeding avoid

Side-effects nausea, vomiting, headache, breast tenderness, changes in body weight, fluid retention, depression, chorea, skin reactions, chloasma, hypertension, may irritate contact lenses, impairment of liver function, hepatic tumours, rarely photosensitivity; see also Combined Hormonal Contraceptives (section 7.3.1)

Licensed use unlicensed for use in children

Indications and dose

See notes above

Induction of sexual maturation in girls

• By mouth

Initially 2 micrograms daily, increasing every 6 months to 5 micrograms, then to 10 micrograms, and then to 20 micrograms daily

Note after 12–18 months of treatment give progestogen for 7 days of each 28-day cycle

Maintenance of sexual maturation in girls

• By mouth

20 micrograms daily with cyclical progestogen for 7 days of each 28-day cycle

Prevention of tall stature in girls

• By mouth

Girls 2–12 years 20–50 micrograms daily

Pituitary priming before growth hormone secretion test in girls

● By mouth

Girls with bone age above 10 years 100 micrograms daily for 3 days before test

Ethinylestradiol (Non-proprietary) (PoM)

Tablets, ethinylestradiol (unlicensed) 10 micrograms, net price 21-tab pack = £139.22; 50 micrograms, 21-tab pack = £139.22; 1 mg, 28-tab pack = £139.22

Note 2 microgram tablets available from 'special-order' manufacturers or specialist-importing companies, see p. 840

Indications and dose

See notes above

Induction and maintenance of sexual maturation in females (combined with an oestrogen after 12–24 months oestrogen therapy)

● By mouth

5 mg once daily for the last 7 days of a 28-day cycle

Postponement of menstruation

● By mouth

5 mg 3 times daily, starting 3 days before expected onset of menstruation

Norethisterone (Non-proprietary) (PoM)

Tablets, norethisterone 5 mg, net price 30-tab pack = £2.04

Primolut N[®] (Bayer) (PoM)

Tablets, norethisterone 5 mg. Net price 30-tab pack = £2.26

Utoylan[®] (Pharmacia) (PoM)

Tablets, norethisterone 5 mg, net price 30-tab pack = £1.40, 90-tab pack = £4.21

6.4.1.2 Progestogens

There are two main groups of progestogen, *progesterone and its analogues* (dydrogesterone and medroxyprogesterone) and *testosterone analogues* (norethisterone and norgestrel). The newer progestogens (desogestrel, norgestimate, and gestodene) are all derivatives of norgestrel; levonorgestrel is the active isomer of norgestrel and has twice its potency. Progesterone and its analogues are less androgenic than the testosterone derivatives and neither progesterone nor dydrogesterone causes virilisation.

In delayed puberty cyclical progestogen is added after 12–18 months of oestrogen therapy (section 6.4.1.1) to establish a menstrual cycle; usually levonorgestrel 30 micrograms or norethisterone 5 mg daily are used for the last 7 days of each 28 day cycle.

Norethisterone is also used to postpone menstruation during a cycle; treatment is started 3 days before the expected onset of menstruation.

NORETHISTERONE

Cautions conditions that may worsen with fluid retention e.g. epilepsy, hypertension, migraine, asthma, cardiac dysfunction; susceptibility to thromboembolism (particular caution with high dose); history of depression; diabetes (monitor closely); **interactions:** Appendix 1 (progestogens)

Contra-indications history of liver tumours, severe liver impairment; severe arterial disease, undiagnosed vaginal bleeding; acute porphyria (section 9.8.2); history during pregnancy of idiopathic jaundice, severe pruritus, or pemphigoid gestationis

Hepatic impairment caution; avoid if severe

Renal impairment use with caution

Pregnancy avoid

Breast-feeding higher doses may suppress lactation and alter milk composition; use lowest effective dose

Side-effects menstrual disturbances, premenstrual-like syndrome (including bloating, fluid retention, breast tenderness), weight gain, nausea, headache, dizziness, insomnia, drowsiness, depression; skin reactions (including urticaria, pruritus, rash, and acne), hirsutism and alopecia; jaundice and anaphylactoid reactions also reported

Licensed use not licensed for use in children

6.4.2 Male sex hormones and antagonists

Androgens cause masculinisation; they are used as replacement therapy in androgen deficiency, in delayed puberty, and in those who are hypogonadal due to either pituitary or testicular disease.

When given to patients with hypopituitarism androgens can lead to normal sexual development and potency but not to fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone (section 6.5.1) which stimulates spermatogenesis as well as androgen production.

Intramuscular depot preparations of **testosterone esters** are preferred for replacement therapy. Testosterone enantate or propionate or alternatively *Sustanon[®]*, which consists of a mixture of testosterone esters and has a longer duration of action, can be used. For induction of puberty, depot testosterone injections are given monthly and the doses increased every 6 to 12 months according to response. Single ester testosterone injections may need to be given more frequently. Implants of testosterone can be used for hypogonadism; the implants are replaced every 4 to 5 months.

Oral **testosterone undecanoate** is used for induction of puberty. An alternative approach that promotes growth rather than sexual maturation uses oral oxandrolone (section 6.4.3).

Chorionic gonadotrophin (section 6.5.1) has also been used in delayed puberty in the male to stimulate endogenous testosterone production, but has little advantage over testosterone.

Caution should be used when androgens or chorionic gonadotrophin are used in treating boys with delayed puberty since the fusion of epiphyses is hastened and may result in short stature.

Testosterone topical gel is also available but experience of use in children under 15 years is limited. Topical testosterone is applied to the penis in the treatment of micropallus; an extemporaneously prepared cream

should be used because the alcohol in proprietary gel formulations causes irritation.

TESTOSTERONE AND ESTERS

Cautions cardiac impairment, hypertension, epilepsy, migraine, diabetes mellitus, skeletal metastases (risk of hypercalcaemia); **interactions:** Appendix 1 (testosterone)

Contra-indications history of primary liver tumours, hypercalcaemia, nephrosis

Hepatic impairment avoid if possible—fluid retention and dose-related toxicity

Renal impairment use with caution—potential for fluid retention

Pregnancy avoid; causes masculinisation of female fetus

Breast-feeding avoid; may cause masculinisation in the female infant or precocious development in the male infant; high doses suppress lactation

Side-effects headache, depression, gastro-intestinal bleeding, nausea, cholestatic jaundice, changes in libido, gynaecomastia, polycythaemia, anxiety, asthenia, paraesthesia, hypertension, electrolyte disturbances including sodium retention with oedema and hypercalcaemia, weight gain; increased bone growth; androgenic effects such as hirsutism, male-pattern baldness, seborrhoea, acne, pruritus; excessive frequency and duration of penile erection, precocious sexual development and premature closure of epiphyses in pre-pubertal males, suppression of spermatogenesis in males and virilism in females; *rarely* liver tumours; sleep apnoea also reported; *with gel*, local irritation and allergic reactions

Licensed use *Sustanon 250*[®] and testosterone enantate not licensed for use in children

Indications and dose

See also under preparations; specialist use only

Induction and maintenance of sexual maturation in males

- By mouth (as testosterone undecanoate)

Child over 12 years 40 mg on alternate days increasing according to response up to 120 mg daily

- By deep intramuscular injection (as testosterone enantate)

Child over 12 years 25–50 mg/m² every month increasing dose every 6–12 months according to response

Treatment of micropallus

- Topically

Apply 3 times daily for 3 weeks

Note Use only specially manufactured preparation (see notes above)

Oral

Restandol[®] Testocaps (MSD) CD4-2

Capsules, orange, testosterone undecanoate 40 mg in oily solution, net price 30-cap pack = £8.55; 60-cap pack = £17.10. Label: 21, 25

Intramuscular

Testosterone Enantate (Non-proprietary) CD4-2

Injection (oily), testosterone enantate 250 mg/mL, net price 1-mL amp = £19.62

Sustanon 250[®] (MSD) CD4-2

Injection (oily), testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, and testosterone decanoate 100 mg/mL, net price 1-mL amp = £2.45

Excipients include arachis (peanut) oil, benzyl alcohol (see Excipients p. 2)

Viormone[®] (Nordic) CD4-2

Injection, testosterone propionate 50 mg/mL, net price 2-mL amp = £4.50

Dose

Delayed puberty in males

- By intramuscular injection
50 mg once weekly

Implant

Testosterone (MSD) CD4-2

Implant, testosterone 100 mg, net price = £9.99; 200 mg = £15.17

Dose

Maintenance of sexual maturation in males

Child over 16 years 100–600 mg; 600 mg usually maintains plasma-testosterone concentration within the normal range for 4–5 months

Cream

Testosterone CD4-2

Cream, testosterone 5% (other strengths available)

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Anti-androgens and precocious puberty

The gonadorelin stimulation test (section 6.5.1) is used to distinguish between *gonadotrophin-dependent (central) precocious puberty* and *gonadotrophin-independent precocious puberty*. Treatment requires specialist management.

Gonadorelin analogues, used in the management of gonadotrophin-dependent precocious puberty, delay development of secondary sexual characteristics and growth velocity.

Testolactone and **cypoterone** are used in the management of gonadotrophin-independent precocious puberty, resulting from McCune-Albright syndrome, familial male precocious puberty (testotoxicosis), hormone-secreting tumours, and ovarian and testicular disorders. Testolactone inhibits the aromatisation of testosterone, the rate limiting step in oestrogen synthesis. Cypoterone is a progestogen with anti-androgen properties.

Spironolactone (section 2.2.3) is sometimes used in combination with testolactone because it has some androgen receptor blocking properties.

High blood concentration of sex hormones may activate release of gonadotrophin releasing hormone, leading to development of secondary, central gonadotrophin-dependent precocious puberty. This may require the addition of gonadorelin analogues to prevent progression of pubertal development and skeletal maturation.

CYPROTERONE ACETATE

Cautions blood counts initially and throughout treatment; monitor adrenocortical function regularly; diabetes mellitus (see also Contra-indications)

Skilled tasks Fatigue and lassitude may impair performance of skilled tasks (e.g. driving)

Contra-indications severe diabetes (with vascular changes), sickle-cell anaemia, liver disease including Dubin-Johnson and Rotor syndromes, previous or existing liver tumours, malignant or wasting diseases, meningioma or history of meningioma, severe depression, history of thromboembolic disorders

Hepatic impairment avoid—dose-related toxicity, see Side-effects below

Side-effects fatigue and lassitude, breathlessness, weight changes, reduced sebum production (may clear acne), changes in hair pattern, gynaecomastia (rarely leading to galactorrhoea and benign breast nodules); rarely hypersensitivity reactions, rash and osteoporosis; inhibition of spermatogenesis (see notes above); hepatotoxicity reported (including jaundice, hepatitis and hepatic failure)

Hepatotoxicity Direct hepatic toxicity such as jaundice, hepatitis and hepatic failure, including fatal cases, have been reported (usually after several months) with cyproterone acetate dosages of 100 mg and above. Liver function tests should be performed before and regularly during treatment and whenever symptoms suggestive of hepatotoxicity occur—if confirmed cyproterone should normally be withdrawn unless the hepatotoxicity can be explained by another cause such as metastatic disease (in which case cyproterone should be continued only if the perceived benefit exceeds the risk)

Licensed use unlicensed for use in children

Indications and dose

Gonadotrophin-independent precocious puberty (specialist use only; see also notes above)

• By mouth

Initially 25 mg twice daily, adjusted according to response

Cyproterone Acetate (Non-proprietary) (PoM)

Tablets, cyproterone acetate 50 mg, net price 56-tab pack = £29.00. Label: 21, counselling, driving

Note 10 mg tablets available from 'special-order' manufacturers or specialist-importing companies, see p. 840

Androcure® (Bayer) (PoM)

Tablets, scored, cyproterone acetate 50 mg, net price 56-tab pack = £29.25. Label: 21, counselling, driving

TESTOLACTONE

Cautions interactions: Appendix 1 (testolactone)

Pregnancy avoid

Breast-feeding no information available

Side-effects nausea, vomiting, anorexia, diarrhoea; hypertension; peripheral neuropathy; weight changes; changes in hair pattern; rarely hypersensitivity reactions, rash

Indications and dose

Gonadotrophin-independent precocious puberty (specialist use only; see also notes above)

• By mouth

5 mg/kg 3–4 times daily; up to 10 mg/kg 4 times daily may be required

Testolactone (PoM)

Tablets, testolactone 50 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

GOSERELIN

Cautions monitor bone mineral density

Contra-indications undiagnosed vaginal bleeding

Pregnancy avoid

Breast-feeding avoid

Side-effects changes in blood pressure, headache, mood changes including depression, hypersensitivity reactions including urticaria, pruritus, rash, asthma and anaphylaxis; changes in scalp and body hair, weight changes, withdrawal bleeding, ovarian cysts (may require withdrawal), breast swelling and tenderness (males and females), visual disturbances, paraesthesia, local reactions at injection site

Licensed use not licensed for use in children

Indications and dose

Gonadotrophin-dependent precocious puberty

See notes above; for doses, see under preparations below

Note Injections may be required more frequently in some cases

Administration Rotate injection site to prevent atrophy and nodule formation

Zoladex® (AstraZeneca) (PoM)

Implant, goserelin (as acetate) 3.6 mg in *Safe-System®* syringe applicator, net price each = £65.00

Dose

- Implant, by subcutaneous injection into anterior abdominal wall
3.6 mg every 28 days

Zoladex® LA (AstraZeneca) (PoM)

Implant, goserelin (as acetate) 10.8 mg in *SafeSystem®* syringe applicator, net price each = £235.00

Dose

- Implant, by subcutaneous injection into anterior abdominal wall
10.8 mg every 12 weeks

LEUPRORELIN ACETATE

Cautions see Goserelin

Contra-indications see Goserelin

Pregnancy avoid—teratogenic in *animal* studies

Breast-feeding avoid

Side-effects see Goserelin

Licensed use not licensed for use in children

Indications and dose

Gonadotrophin-dependent precocious puberty

See notes above; for doses, see under preparations below

Note Injections may be required more frequently in some cases

Administration Rotate injection site to prevent atrophy and nodule formation

Prostap® SR (Wyeth) (PoM)

Injection (microsphere powder for reconstitution), leuporelin acetate, net price 3.75-mg vial with 1-mL vehicle-filled syringe = £75.24

Dose

- By subcutaneous or by intramuscular injection
3.75 mg every four weeks (half this dose is sometimes used in children with body-weight under 20 kg)

Prostap® 3 (Wyeth) (PoM)

Injection (microsphere powder for reconstitution), leuporelin acetate, net price 11.25-mg vial with 2-mL vehicle-filled syringe = £225.72

Dose

- By subcutaneous or by intramuscular injection
11.25 mg every 12 weeks

TRIPTORELIN

Cautions see Goserelin

Contra-indications see Goserelin

Pregnancy avoid

Breast-feeding avoid

Side-effects see Goserelin; also gastro-intestinal disturbances; asthenia; arthralgia

Indications and dose**Gonadotrophin-dependent precocious puberty**

See notes above; for doses, see under preparations below

Administration rotate injection site to prevent atrophy and nodule formation

Decapeptyl® SR (Ipsen) (PoM)

Injection, (powder for suspension), m/r, triptorelin (as acetate), net price 11.25-mg vial (with diluent) = £207.00

Dose

- By intramuscular injection
11.25 mg every 3 months
- Note** Each vial includes an overage to allow accurate administration of 11.25 mg dose

Gonapeptyl® Depot (Ferring) (PoM)

Injection (powder for suspension), triptorelin (as acetate), net price 3.75-mg prefilled syringe (with prefilled syringe of vehicle) = £81.69

Dose

- By subcutaneous or intramuscular injection
Body-weight under 20 kg initially 1.875 mg on days 0, 14, and 28, then 1.875 mg every 4 weeks
Body-weight 20–30 kg initially 2.5 mg on days 0, 14, and 28, then 2.5 mg every 4 weeks
Body-weight over 30 kg initially 3.75 mg on days 0, 14, and 28, then 3.75 mg every 4 weeks; discontinue when bone maturation consistent with age over 12 years in girls and over 13 years in boys
Note May be given every 3 weeks if necessary

6.4.3 Anabolic steroids

Anabolic steroids have some androgenic activity but in girls they cause less virilisation than androgens. They are used in the treatment of some *aplastic anaemias* (section 9.1.3). Oxandrolone is used to stimulate late pre-pubertal growth prior to induction of sexual maturation in boys with short stature and in girls with Turner's syndrome; specialist management is required.

OXANDROLONE

Cautions see Testosterone (section 6.4.2); **interactions:** Appendix 1 (oxandrolone)

Contra-indications see Testosterone (section 6.4.2)

Hepatic impairment see Testosterone (section 6.4.2)

Renal impairment see Testosterone (section 6.4.2)

Pregnancy see Testosterone (section 6.4.2)

Breast-feeding see Testosterone (section 6.4.2)

Side-effects see Testosterone (section 6.4.2)

Indications and dose**Stimulation of late pre-pubertal growth in boys with short stature**

- By mouth
Boys 10–18 years (or appropriate age) 1.25–2.5 mg daily for 3–6 months

Stimulation of late pre-pubertal growth in girls with Turner's syndrome

- By mouth
Girls in combination with growth hormone 0.625–2.5 mg daily

Oxandrolone

Tablets, oxandrolone 2.5 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

6.5 Hypothalamic and pituitary hormones**6.5.1 Hypothalamic and anterior pituitary hormones including growth hormone****6.5.2 Posterior pituitary hormones and antagonists**

Use of preparations in these sections requires detailed prior investigation of the patient and *should be reserved for specialist centres*.

6.5.1 Hypothalamic and anterior pituitary hormones including growth hormone**Anterior pituitary hormones****Corticotrophins**

Tetracosactide (tetracosactrin), an analogue of corticotropin (adrenocorticotrophic hormone, ACTH), is used to test adrenocortical function; failure of plasma-cortisol concentration to rise after administration of tetracosactide indicates adrenocortical insufficiency. A low-dose test is considered by some clinicians to be more sensitive when used to confirm established, partial adrenal suppression.

Tetracosactide should be given only if no other ACTH preparations have been given previously. Tetracosactide depot injection (*Synacthen Depot®*) is also used in the treatment of infantile spasms (see Infantile spasms, section 4.8.1) but it is contra-indicated in neonates because of the presence of benzyl alcohol in the injection. Corticotropin-releasing factor, corticorelin, (also known as corticotropin-releasing hormone, CRH) is

used to test anterior pituitary function and secretion of corticotropin.

TETRACOSACTIDE (Tetracosactrin)

Cautions as for corticosteroids, section 6.3.2; **important:** risk of anaphylaxis (medical supervision; consult product literature); history of atopic allergy (e.g. asthma, eczema, hayfever); history of hypersensitivity; **interactions:** Appendix 1 (corticosteroids)

Contra-indications as for corticosteroids, section 6.3.2; avoid injections containing benzyl alcohol in neonates (see under preparations); history of hypersensitivity to corticotrophins

Hepatic impairment see section 6.3.2

Renal impairment see section 6.3.2

Pregnancy avoid (but may be used diagnostically if essential)

Breast-feeding avoid (but may be used diagnostically if essential)

Side-effects as for corticosteroids, section 6.3.2

Licensed use not licensed for low-dose test for adrenocortical insufficiency or treatment of infantile spasms

Indications and dose

See notes above and under preparations below

Synacthen® (Alliance) (PoM)

Injection, tetracosactide 250 micrograms (as acetate)/mL. Net price 1-mL amp = £2.93
Dose

Diagnosis of adrenocortical insufficiency (30-minute test)

- By intramuscular or intravenous injection
Standard-dose test 145 micrograms/m² (max. 250 micrograms) as a single dose
Low-dose test 300 nanograms/m² as a single dose
Administration may be diluted in sodium chloride 0.9% to 250 nanograms/mL

Synacthen Depot® (Alliance) (PoM)

Injection (aqueous suspension), tetracosactide acetate 1 mg/mL, with zinc phosphate complex. Net price 1-mL amp = £4.18

Excipients include benzyl alcohol (avoid in neonates, see Excipients p. 2)

Dose

Infantile spasms

- By intramuscular injection
Child 1 month–2 years initially 500 micrograms on alternate days, adjusted according to response

CORTICORELIN

(Corticotrophin-releasing hormone, CRH)

Pregnancy avoid

Breast-feeding avoid

Side-effects flushing of face, neck and upper body, hypotension, mild sensation of taste or smell

Licensed use not licensed

Indications and dose

Test of anterior pituitary function

- By intravenous injection over 30 seconds
Child 1 month–18 years 1 microgram/kg (max. 100 micrograms) as a single dose

CRH Ferring® (Shire) (PoM)

Injection, corticorelin 100 micrograms

Gonadotrophins

Gonadotrophins are occasionally used in the treatment of hypogonadotrophic hypogonadism and associated oligospermia. There is no justification for their use in primary gonadal failure.

Chorionic gonadotrophin is used in the investigation of testicular function in suspected primary hypogonadism and incomplete masculinisation. It has also been used in delayed puberty in boys to stimulate endogenous testosterone production, but it has little advantage over testosterone (section 6.4.2).

CHORIONIC GONADOTROPHIN (Human Chorionic Gonadotrophin; HCG)

A preparation of a glycoprotein fraction secreted by the placenta and obtained from the urine of pregnant women having the action of the pituitary luteinising hormone

Cautions cardiac impairment, asthma, epilepsy, migraine; prepubertal boys (risk of premature epiphyseal closure or precocious puberty)

Contra-indications androgen-dependent tumours

Renal impairment use with caution

Side-effects oedema (reduce dose), headache, tiredness, mood changes, gynaecomastia, local reactions

Licensed use unlicensed in children for test of testicular function

Indications and dose

Test of testicular function

- By intramuscular injection

Short stimulation test:

Child 1 month–18 years 1500–2000 units once daily for 3 days

Prolonged stimulation test:

Child 1 month–18 years 1500–2000 units twice weekly for 3 weeks

Hypogonadotrophic hypogonadism

- By intramuscular injection

Child 1 month–18 years 1000–2000 units twice weekly, adjusted to response

Undescended testes

- By intramuscular injection

Child 7–18 years initially 500 units 3 times weekly (1000 units twice weekly if over 17 years); adjusted to response; up to 4000 units 3 times weekly may be required; continue for 1–2 months after testicular descent

Choragon® (Ferring) (CD4-2)

Injection, powder for reconstitution, chorionic gonadotrophin. Net price 5000-unit amp (with solvent) = £3.26. For intramuscular injection

Pregnyl® (MSD) (CD4-2)

Injection, powder for reconstitution, chorionic gonadotrophin. Net price 1500-unit amp = £2.12; 5000-unit amp = £3.15 (both with solvent). For subcutaneous or intramuscular injection

Growth hormone

Growth hormone is used to treat proven deficiency of the hormone, Prader-Willi syndrome, Turner's syndrome, growth disturbance in children born small for corrected gestational age, chronic renal insufficiency, and short stature homeobox-containing gene (SHOX) deficiency (see NICE guidance below). Growth

hormone is also used in Noonan syndrome and idiopathic short stature [unlicensed indications] under specialist management. Treatment should be initiated and monitored by a paediatrician with expertise in managing growth-hormone disorders; treatment can be continued under a shared-care protocol by a general practitioner.

Growth hormone of human origin (HGH; somatotrophin) has been replaced by a growth hormone of human sequence, **somatropin**, produced using recombinant DNA technology.

NICE guidance

Somatropin for the treatment of growth failure in children (May 2010)

Somatropin is recommended for children with growth failure who:

- have growth-hormone deficiency;
- have Turner's syndrome;
- have Prader-Willi syndrome;
- have chronic renal insufficiency;
- are born small for corrected gestational age with subsequent growth failure at 4 years of age or later;
- have short stature homeobox-containing gene (SHOX) deficiency.

Treatment should be discontinued if growth velocity increases by less than 50% from baseline in the first year of treatment.

www.nice.org.uk/TA188

Mecasermin, a human insulin-like growth factor-I (rhIGF-I), is licensed to treat growth failure in children with severe primary insulin-like growth factor-I deficiency (section 6.7.4).

SOMATROPIN

(Recombinant Human Growth Hormone)

Cautions diabetes mellitus (adjustment of antidiabetic therapy may be necessary), papilloedema (see under Side-effects), relative deficiencies of other pituitary hormones (notably hypothyroidism—manufacturers recommend periodic thyroid function tests but limited evidence of clinical value), history of malignant disease, disorders of the epiphysis of the hip (monitor for limping), resolved intracranial hypertension (monitor closely), initiation of treatment close to puberty not recommended in child born small for corrected gestational age; Silver-Russell syndrome; rotate subcutaneous injection sites to prevent lipoatrophy; **interactions:** Appendix 1 (somatropin)

Contra-indications evidence of tumour activity (complete antitumour therapy and ensure intracranial lesions inactive before starting); not to be used after renal transplantation or for growth promotion in children with closed epiphyses (or near closure in Prader-Willi syndrome); severe obesity or severe respiratory syndrome in Prader-Willi syndrome

Pregnancy interrupt treatment if pregnancy occurs

Breast-feeding absorption from milk unlikely

Side-effects headache, funduscopy for papilloedema recommended if severe or recurrent headache, visual problems, nausea and vomiting occur—if papilloedema confirmed consider benign intracranial hypertension (rare cases reported); fluid retention (peripheral oedema), arthralgia, myalgia, carpal tunnel syndrome, paraesthesia, antibody formation, hypothyroidism, insulin resistance, hyperglycaemia, hypoglycaemia, reactions at injection site; leukaemia in children with growth hormone deficiency also reported

Licensed use not licensed for use in Noonan syndrome

Indications and dose

Gonadal dysgenesis (Turner's syndrome)

- By subcutaneous injection
45–50 micrograms/kg daily or 1.4 mg/m² daily

Deficiency of growth hormone

- By subcutaneous or intramuscular injection
23–39 micrograms/kg daily or 0.7–1 mg/m² daily

Prader-Willi syndrome

- By subcutaneous injection
Children with growth velocity greater than 1 cm/year in combination with energy-restricted diet, 35 micrograms/kg daily or 1 mg/m² daily; max. 2.7 mg daily

Chronic renal insufficiency (renal function decreased to less than 50%)

- By subcutaneous injection
45–50 micrograms/kg daily or 1.4 mg/m² daily (higher doses may be needed) adjusted if necessary after 6 months

Growth disturbance in children born small for corrected gestational age whose growth has not caught up by 4 years of age or later; Noonan syndrome

- By subcutaneous injection
35 micrograms/kg daily or 1 mg/m² daily

SHOX deficiency

- By subcutaneous injection
45–50 micrograms/kg daily

Genotropin® (Pharmacia) (CD4-2)

Injection, two-compartment cartridge containing powder for reconstitution, somatropin (rbe) and diluent, net price 5.3-mg (16-unit) cartridge = £92.15; 12-mg (36-unit) cartridge = £208.65. For use with **Genotropin® Pen** (JMS) device (available free of charge from clinics). For subcutaneous injection

GoQuick® injection, two-compartment, multi-dose disposable, prefilled pen containing powder for reconstitution, somatropin (rbe) and diluents, net price 5.3-mg (16-unit) prefilled pen = £92.15; 12-mg (36-unit) prefilled pen = £208.65. For subcutaneous injection

MiniQuick® injection, two-compartment single-dose syringe containing powder for reconstitution, somatropin (rbe) and diluent, net price 0.2-mg (0.6-unit) syringe = £3.48; 0.4-mg (1.2-unit) syringe = £6.95; 0.6-mg (1.8-unit) syringe = £10.43; 0.8-mg (2.4-unit) syringe = £13.91; 1-mg (3-unit) syringe = £17.39; 1.2-mg (3.6-unit) syringe = £20.87; 1.4-mg (4.2-unit) syringe = £24.34; 1.6-mg (4.8-unit) syringe = £27.82; 1.8-mg (5.4-unit) syringe = £31.30; 2-mg (6-unit) syringe = £34.77. For subcutaneous injection

Humatrope® (Lilly) (CD4-2)

Injection, powder for reconstitution, somatropin (rbe), net price 6-mg (18-unit) cartridge = £108.00; 12-mg (36-unit) cartridge = £216.00; 24-mg (72-unit) cartridge = £432.00; all supplied with diluent. For subcutaneous or intramuscular injection; cartridges for subcutaneous injection

Norditropin® (Novo Nordisk) CD4-2

SimpleXx® injection, somatropin (epi) 3.3 mg (10 units)/mL, net price 1.5-mL (5-mg, 15-unit) cartridge = £106.35; 6.7 mg (20 units)/mL, 1.5-mL (10-mg, 30-unit) cartridge = £212.70; 10 mg (30 units)/mL, 1.5-mL (15-mg, 45-unit) cartridge = £319.05. For use with appropriate *NordiPen®* JMS device (available free of charge from clinics). For subcutaneous injection

Nordiflex® injection, multidose disposable prefilled pen, somatropin (rbe) 10 mg (30 units)/mL, net price 1.5-mL (15-mg, 45-unit) prefilled pen = £347.70. For use with *NovoFine®* or *NovoTwist®* needles. For subcutaneous injection

NutropinAq® (Ipsen) CD4-2

Injection, somatropin (rbe), net price 10 mg (30 units) 2-mL cartridge = £203.00. For use with *NutropinAq®* Pen JMS device (available free of charge from clinics). For subcutaneous injection

Omnitrope® (Sandoz) CD4-2

Injection, somatropin (rbe) 3.3 mg (10 units)/mL, net price 1.5 mL (5-mg, 15-unit) cartridge = £73.75; 6.7 mg (20 units)/mL, 1.5 mL (10-mg, 30-unit) cartridge = £147.50. For use with *Omnitrope Pen 5®* JMS and *Omnitrope Pen 10®* JMS devices respectively (available free of charge from clinics). For subcutaneous injection

Excipients include benzyl alcohol (in 5-mg cartridge) (avoid in neonates, see Excipients, p. 2)

Note Biosimilar medicine, see p. 2

Saizen® (Merck Serono) CD4-2

Injection, somatropin (rmc), 5.83 mg (17.5 units)/mL, net price 1.03-mL (6-mg, 18-unit) cartridge = £139.08; 8 mg (24 units)/mL, 1.5-mL (12-mg, 36-unit) cartridge = £278.16, 2.5-mL (20-mg, 60-unit) cartridge = £463.60. For use with *cool.click®* JMS needle-free autoinjector device or *easypod®* JMS autoinjector device (available free of charge from clinics). For subcutaneous injection

Click.easy®, powder for reconstitution, somatropin (rmc), net price 8-mg (24-unit) vial (in *Click.easy®* device with diluent) = £185.44. For use with *One.click®* JMS autoinjector device or *cool.click®* JMS needle-free autoinjector device or *easypod®* JMS autoinjector device (available free of charge from clinics). For subcutaneous injection

Zomacton® (Ferring) CD4-2

Injection, powder for reconstitution, somatropin (rbe), net price 4-mg (12-unit) vial (with diluent) = £79.69. For use with *ZomaJet 2 Vision®* JMS needle-free device (available free of charge from clinics) or with needles and syringes; 10-mg (30-unit) vial (with diluent) = £199.23, for use with *ZomaJet Vision X®* JMS needle-free device (available free of charge from clinics) or with needles and syringes. For subcutaneous injection

Excipients include benzyl alcohol (in 4-mg vial) (avoid in neonates, see Excipients, p. 2)

Other growth hormone stimulation tests involve the use of insulin, glucagon, arginine, and clonidine [all unlicensed uses]. The tests should be carried out in specialist centres.

GONADORELIN

(Gonadotrophin-releasing hormone; GnRH; LH–RH)

Cautions pituitary adenoma

Pregnancy avoid

Breast-feeding avoid

Side-effects rarely nausea, headache, abdominal pain, increased menstrual bleeding; rarely, hypersensitivity reaction on repeated administration of large doses; irritation at injection site

Licensed use not licensed for use in children under 1 year

Indications and dose

Assessment of anterior pituitary function; assessment of delayed puberty

- By subcutaneous or intravenous injection

Child 1–18 years 2.5 micrograms/kg (max. 100 micrograms) as a single dose

Gonadorelin® (Intrapharm) PoM

Reconstitution, powder for reconstitution, gonadorelin.

Net price 100-microgram vial (with diluent) = £67.00 (hosp. only)

Excipients include benzyl alcohol (avoid in neonates, see Excipients p. 2)

6.5.2 Posterior pituitary hormones and antagonists

Posterior pituitary hormones

Diabetes insipidus Diabetes insipidus is caused by either a deficiency of anti-diuretic hormone (ADH, vasopressin) secretion (cranial, neurogenic, or pituitary diabetes insipidus) or by failure of the renal tubules to react to secreted antidiuretic hormone (nephrogenic diabetes insipidus).

Vasopressin (antidiuretic hormone, ADH) is used in the treatment of *pituitary diabetes insipidus* as is its analogue **desmopressin**. Dosage is tailored to produce a regular diuresis every 24 hours to avoid water intoxication. Treatment may be required permanently or for a limited period only in diabetes insipidus following trauma or pituitary surgery.

Desmopressin is more potent and has a longer duration of action than vasopressin; unlike vasopressin it has no vasoconstrictor effect. It is given by mouth or intranasally for maintenance therapy, and by injection in the postoperative period or in unconscious patients. Desmopressin is also used in the differential diagnosis of diabetes insipidus; following an intramuscular or intranasal dose, restoration of the ability to concentrate urine after water deprivation confirms a diagnosis of pituitary diabetes insipidus. Failure to respond suggests nephrogenic diabetes insipidus. Fluid input must be managed carefully to avoid hyponatraemia; this test is not usually recommended in young children.

In *nephrogenic* and *partial pituitary diabetes insipidus* benefit may be gained from the paradoxical antidiuretic

effect of thiazides (section 2.2.1) e.g. chlorothiazide 10–20 mg/kg (max. 500 mg) twice daily.

Other uses Desmopressin is also used to boost factor VIII concentration in mild to moderate haemophilia and in von Willebrand's disease; it is also used to test fibrinolytic response. For a comment on use of desmopressin in nocturnal enuresis see section 7.4.2.

Vasopressin infusion is used to control variceal bleeding in portal hypertension, before introducing more definitive treatment. **Terlipressin**, a derivative of vasopressin with reportedly less pressor and antidiuretic activity, and octreotide are used similarly but experience in children is limited.

DESMOPRESSIN

Cautions see under Vasopressin; less pressor activity, but still considerable caution in cardiovascular disease and in hypertension (not indicated for nocturnal enuresis or nocturia in these circumstances); also considerable caution in cystic fibrosis; in nocturia and nocturnal enuresis limit fluid intake from 1 hour before dose until 8 hours afterwards; in nocturia periodic blood pressure and weight checks needed to monitor for fluid overload; **interactions:** Appendix 1 (desmopressin)

For cautions specifically relating to the use of desmopressin in nocturnal enuresis see section 7.4.2

Hyponatraemic convulsions Patients being treated for primary nocturnal enuresis should be warned to avoid fluid overload (including during swimming) and to stop taking desmopressin during an episode of vomiting or diarrhoea (until fluid balance normal). The risk of hyponatraemic convulsions can also be minimised by keeping to the recommended starting doses and by avoiding concomitant use of drugs which increase secretion of vasopressin (e.g. tricyclic antidepressants)

Contra-indications cardiac insufficiency and other conditions treated with diuretics; psychogenic polydipsia and polydipsia in alcohol dependence

Renal impairment use with caution; antidiuretic effect may be reduced

Pregnancy small oxytocic effect in third trimester; increased risk of pre-eclampsia

Breast-feeding amount too small to be harmful

Side-effects fluid retention, and hyponatraemia (in more serious cases with convulsions) on administration without restricting fluid intake; stomach pain, headache, nausea, vomiting, allergic reactions, and emotional disturbance in children also reported; epistaxis, nasal congestion, rhinitis with nasal spray

Licensed use consult product literature for individual preparations; not licensed for assessment of antidiuretic hormone secretion

Indications and dose

Assessment of antidiuretic hormone secretion (congenital deficiency suspected) (specialist use only)

• Intranasally

Child 1 month–2 years initially 100–500 nanograms as a single dose

Assessment of antidiuretic hormone secretion (congenital deficiency not suspected) (specialist use only)

• Intranasally

Child 1 month–2 years 1–5 micrograms as a single dose

Test for suspected diabetes insipidus (water deprivation test)

• Intranasally

Neonate not recommended, use trial of treatment

Child 1 month–2 years 5–10 micrograms as a single dose; not usually recommended, see notes above

Child 2–12 years 10–20 micrograms as a single dose, see notes above

Child 12–18 years 20 micrograms as a single dose, see notes above

• By subcutaneous or intramuscular injection

Neonate not recommended, use trial of treatment

Child 1 month–2 years 400 nanograms as a single dose; not usually recommended, see notes above

Child 2–12 years 0.5–1 microgram as a single dose, see notes above

Child 12–18 years 1–2 micrograms as a single dose, see notes above

Diabetes insipidus, treatment

• By mouth

(as desmopressin acetate)

Neonate initially 1–4 micrograms 2–3 times daily, adjusted according to response

Child 1 month–2 years initially 10 micrograms 2–3 times daily, adjusted according to response (range 30–150 micrograms daily)

Child 2–12 years initially 50 micrograms 2–3 times daily, adjusted according to response (range 100–800 micrograms daily)

Child 12–18 years initially 100 micrograms 2–3 times daily, adjusted according to response (range 0.2–1.2 mg daily)

• Sublingually

(as desmopressin base)

Child 2–18 years initially 60 micrograms 3 times daily, adjusted according to response (range 40–240 micrograms 3 times daily)

• Intranasally

(as desmopressin acetate)

Neonate initially 100–500 nanograms, adjusted according to response (range 1.25–10 micrograms daily in 1–2 divided doses)

Child 1 month–2 years initially 2.5–5 micrograms 1–2 times daily, adjusted according to response

Child 2–12 years initially 5–20 micrograms 1–2 times daily, adjusted according to response

Child 12–18 years initially 10–20 micrograms 1–2 times daily, adjusted according to response

• By subcutaneous or intramuscular injection

Neonate initially 100 nanograms once daily, adjusted according to response (intramuscular route only)

Child 1 month–12 years initially 400 nanograms once daily, adjusted according to response

Child 12–18 years initially 1–4 micrograms once daily, adjusted according to response

Primary nocturnal enuresis● **By mouth**

(as desmopressin acetate)

Child 5–18 years 200 micrograms at bedtime, increased to 400 micrograms at bedtime only if lower dose not effective (**important**: see also Cautions), reassess after 3 months by withdrawing treatment for at least 1 week

● **Sublingually**

(as desmopressin base)

Child 5–18 years 120 micrograms at bedtime, increased to 240 micrograms at bedtime only if lower dose not effective (**important**: see also Cautions); reassess after 3 months by withdrawing treatment for at least 1 week

Fibrinolytic response testing● **By intravenous injection over 20 minutes or by subcutaneous injection**

Child 2–18 years 300 nanograms/kg as a single dose; blood sampled after 20 minutes for fibrinolytic activity

Mild to moderate haemophilia and von Willebrand's disease● **By intravenous infusion over 20 minutes or by subcutaneous injection**

Child 1 month–18 years 300 nanograms/kg as a single dose immediately before surgery or after trauma; may be repeated at intervals of 12 hours if no tachycardia

● **Intranasally**

Child 1–18 years 4 micrograms/kg as a single dose, for pre-operative use give 2 hours before procedure

Renal function testing● **Intranasally**

Child 1 month–1 year 10 micrograms (empty bladder at time of administration and restrict fluid intake to 50% at next 2 feeds to avoid fluid overload)

Child 1–15 years 20 micrograms (empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload)

Child 15–18 years 40 micrograms (empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload)

● **By subcutaneous or intramuscular injection**

Child 1 month–1 year 400 nanograms (empty bladder at time of administration and restrict fluid intake to 50% at next 2 feeds to avoid fluid overload)

Child 1–18 years 2 micrograms (empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload)

Desmopressin acetate (Non-proprietary) ^(PoM)

Tablets, desmopressin acetate 100 micrograms, net price 90-tab pack = £60.12; 200 micrograms, 30-tab pack = £9.02, 90-tab pack = £39.20. Counselling, fluid intake, see above

Nasal spray, desmopressin acetate 10 micrograms/metered spray, net price 6-mL unit (60 metered sprays) = £9.34. Counselling, fluid intake, see above

Brands include Presinex[®]

Note Children requiring dose of less than 10 micrograms should be given DDAVP[®] intranasal solution

DDAVP[®] (Ferring) ^(PoM)

Tablets, both scored, desmopressin acetate 100 micrograms, net price 90-tab pack = £44.12; 200 micrograms, 90-tab pack = £88.23. Counselling, fluid intake, see above

Note Tablets may be crushed

Oral lyophilisates, (DDAVP[®] Melt), desmopressin (as acetate) 60 micrograms, net price 100-tab pack = £50.53; 120 micrograms, 100-tab pack = £101.07; 240 micrograms, 100-tab pack = £202.14. For sublingual administration. Label: 26, counselling, fluid intake, see notes above

Intranasal solution, desmopressin acetate 100 micrograms/mL. Net price 2.5-mL dropper bottle and catheter = £9.72. Counselling, fluid intake, see above

Administration May be diluted with Sodium Chloride 0.9% to a concentration of 10 micrograms/mL

Injection, desmopressin acetate 4 micrograms/mL. Net price 1-mL amp = £1.32

Administration May be administered orally [unlicensed]; for intravenous infusion, higher doses used in mild to moderate haemophilia and von Willebrand's disease may be diluted with 30–50 mL Sodium Chloride 0.9% intravenous infusion

Desmomet[®] (Ferring) ^(PoM)

Oral lyophilisates, desmopressin (as acetate) 120 micrograms, net price 30-tab pack = £30.34; 240 micrograms, 30-tab pack = £60.68. For sublingual administration. Label: 26, counselling, fluid intake, see above

Desmotabs[®] (Ferring) ^(PoM)

Tablets, scored, desmopressin acetate 200 micrograms, net price 30-tab pack = £29.43. Counselling, fluid intake, see above

Note tablets may be crushed

Desmospray[®] (Ferring) ^(PoM)

Nasal spray, desmopressin acetate 10 micrograms/metered spray, net price 6-mL unit (60 metered sprays) = £25.02. Counselling, fluid intake, see above

Note Children requiring dose of less than 10 micrograms should be given DDAVP[®] intranasal solution

Low dose Desmospray[®] ^(PoM)

Nasal spray, desmopressin acetate 2.5 micrograms/metered spray
Available from Ferring on a named-patient basis

Octim[®] (Ferring) ^(PoM)

Nasal spray, desmopressin acetate 150 micrograms/metered spray, net price 2.5-mL unit (25 metered sprays) = £576.60. Counselling, fluid intake, see above

Injection, desmopressin acetate 15 micrograms/mL, net price 1-mL amp = £19.22

Administration for intravenous infusion dilute with 50 mL of Sodium Chloride 0.9% and give over 20 minutes

TERLIPRESSIN ACETATE

Cautions uncontrolled hypertension; vascular disease; heart disease; history of QT-interval prolongation; concomitant use of drugs that prolong the QT-interval; arrhythmia; respiratory disease; septic shock; electrolyte and fluid disturbances

Renal impairment use with caution in chronic renal failure

Pregnancy avoid unless benefits outweigh risk—uterine contractions and increased intra-uterine pressure in early pregnancy, and decreased uterine blood flow reported

Breast-feeding avoid unless benefits outweigh risk—no information available

Side-effects abdominal cramps, diarrhoea, hypertension, hypotension, peripheral ischaemia, pallor, arrhythmia, bradycardia, headache; *less commonly* nausea, vomiting, hot flushes, angina, myocardial infarction, tachycardia, intestinal ischaemia, bronchospasm, respiratory failure, pulmonary oedema, convulsions, hyponatraemia; *rarely* dyspnoea; *very rarely* stroke, hyperglycaemia; *also reported* heart failure, skin necrosis

Licensed use unlicensed for use in children

Indications and dose

See under preparations

Glypressin® (Ferring) (PoM)

Injection, powder for reconstitution, terlipressin acetate, net price 1-mg vial with 5 mL diluent = £18.47

Injection, solution for injection, terlipressin acetate, 0.12 mg/mL, net price 1-mg (8.5 mL) amp = £19.39

Dose
Adjunct in acute massive haemorrhage of gastro-intestinal tract or oesophageal varices (specialist use only)

- By intravenous injection

Child 12–18 years, 2 mg every 4 hours until bleeding controlled (after initial dose, may reduce to 1 mg every 4 hours if not tolerated or body-weight under 50 kg); max. duration 48 hours

Varique® (Sinclair IS) (PoM)

Injection, powder for reconstitution, terlipressin acetate, net price 1-mg vial with 5 mL diluent = £17.90

Dose

Adjunct in acute massive haemorrhage of gastro-intestinal tract or oesophageal varices (specialist use only)

- By intravenous injection over 1 minute

Child 12–18 years initially 1 mg if body-weight under 50 kg (initial dose 1.5 mg if body-weight 50–70 kg, or 2 mg if body-weight over 70 kg), then 1 mg every 4–6 hours for up to 72 hours

VASOPRESSIN

Cautions heart failure, hypertension, asthma, epilepsy, migraine or other conditions which might be aggravated by water retention; avoid fluid overload

Contra-indications vascular disease (especially disease of coronary arteries) unless extreme caution, chronic nephritis (until reasonable blood nitrogen concentrations attained)

Renal impairment see Contra-indications

Pregnancy oxytocic effect in third trimester

Breast-feeding not known to be harmful

Side-effects fluid retention, pallor, tremor, sweating, vertigo, headache, nausea, vomiting, belching, abdominal cramps, desire to defaecate, hypersensitivity reactions (including anaphylaxis), constriction of coronary arteries (may cause anginal attacks and myocardial ischaemia), peripheral ischaemia and rarely gangrene

Licensed use not licensed for use in children

Indications and dose

Adjunct in acute massive haemorrhage of gastro-intestinal tract or oesophageal varices (specialist use only)

- By continuous intravenous infusion (may also be infused directly into the superior mesenteric artery)

Child 1 month–18 years initially 0.3 units/kg (max. 20 units) over 20–30 minutes *then* 0.3 units/kg/hour, adjusted according to response (max. 1 unit/kg/hour); if bleeding stops, continue at same dose for 12 hours, then withdraw gradually over 24–48 hours; max. duration of treatment 72 hours

Administration for *intravenous infusion* dilute with Glucose 5% or Sodium Chloride 0.9% to a concentration of 0.2–1 unit/mL

■ Synthetic vasopressin

Argipressin (Non-proprietary) (PoM)

Injection, argipressin (synthetic vasopressin) 20 units/mL, net price 1-mL amp = £22.50 (hosp. only)

6.6 Drugs affecting bone metabolism

6.6.1 Calcitonin

6.6.2 Bisphosphonates

The two main disorders of bone metabolism that occur in children are rickets and osteoporosis. The two most common forms of rickets are Vitamin D deficiency rickets (section 9.6.4) and hypophosphataemic rickets (section 9.5.2). See also calcium (section 9.5.1.1).

Osteoporosis

Osteoporosis in children may be primary (e.g. *osteogenesis imperfecta* and *idiopathic juvenile osteoporosis*), or secondary (e.g. due to inflammatory disorders, immobilisation, or corticosteroids); specialist management is required.

Corticosteroid-induced osteoporosis To reduce the risk of osteoporosis doses of oral corticosteroids should be as low as possible and courses of treatment as short as possible.

6.6.1 Calcitonin

Calcitonin is involved with parathyroid hormone in the regulation of bone turnover and hence in the maintenance of calcium balance and homeostasis. **Calcitonin (salmon)** (**salcatonin**, synthetic or recombinant salmon calcitonin) is used by specialists to lower the plasma-calcium concentration in children with hypercalcaemia associated with malignancy.

CALCITONIN (SALMON)/SALCATIONIN

Cautions history of allergy (skin test advised); heart failure; avoid prolonged use—risk of malignancy (use lowest effective dose for shortest possible time); monitor bone growth

Contra-indications hypocalcaemia

Renal impairment use with caution

Pregnancy avoid unless essential, toxicity in *animal* studies

Breast-feeding avoid unless essential, may inhibit lactation

Side-effects nausea, vomiting, diarrhoea, abdominal pain, taste disturbance, flushing, dizziness, headache, fatigue, malignancy (with long-term use) musculo-skeletal pain; *less commonly* hypertension, oedema, cough, polyuria, visual disturbances, injection-site reactions, rash, hypersensitivity reactions including pruritus; *also reported* tremor

Licensed use not licensed in children

Indications and dose

Hypercalcaemia (experience limited in children) (specialist use only)

- By subcutaneous or intramuscular injection

Child 1 month–18 years 2.5–5 units/kg every 12 hours, max. 400 units every 6–8 hours, adjusted according to response (no additional benefit with over 8 units/kg every 6 hours)

- By slow intravenous infusion

Child 1 month–18 years 5–10 units/kg over at least 6 hours

Osteoporosis (specialist use only)

Refer for specialist advice, experience very limited

Administration for *intravenous infusion*, dilute injection solution (e.g. 400 units in 500 mL) with Sodium Chloride 0.9% and give over at least 6 hours; glass or hard plastic containers should not be used; some loss of potency on dilution and administration—use diluted solution without delay

Miacalcic® (Novartis) (PoM)

Injection, calcitonin (salmon) 50 units/mL, net price 1-mL amp = £3.42; 100 units/mL, 1-mL amp = £6.84; 200 units/mL, 2-mL vial = £24.60

6.6.2 Bisphosphonates

Bisphosphonates are adsorbed on to hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover.

A bisphosphonate such as **pamidronate disodium** is used in the management of severe forms of *osteogenesis imperfecta* and other causes of osteoporosis in children to reduce the number of fractures; the long-term effects of bisphosphonates in children have not been established. Single doses of bisphosphonates are also used to manage hypercalcaemia (section 9.5.1.2). Treatment should be initiated under specialist advice **only**.

Bisphosphonates: osteonecrosis of the jaw

The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease.

Risk factors for developing osteonecrosis of the jaw that should be considered are: potency of bisphosphonate (highest for zoledronate), route of administration, cumulative dose, duration and type of malignant disease, concomitant treatment, smoking, comorbid conditions, and history of dental disease.

All patients should have a dental check-up (and any necessary remedial work should be performed) before bisphosphonate treatment, or as soon as possible after starting treatment.

During bisphosphonate treatment patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms.

Guidance for dentists in primary care is included in *Oral Health Management of Patients Prescribed Bisphosphonates: Dental Clinical Guidance*, Scottish Dental Clinical Effectiveness Programme, April 2011 (available at www.sdcep.org.uk).

MHRA/CHM advice

Bisphosphonates: atypical femoral fractures (June 2011)

Atypical femoral fractures have been reported rarely with bisphosphonate treatment, mainly in patients receiving long-term treatment for osteoporosis.

The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on an assessment of the benefits and risks of treatment for individual patients, particularly after 5 or more years of use.

Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate.

Discontinuation of bisphosphonate treatment in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.

ALENDRONIC ACID

Cautions upper gastro-intestinal disorders (dysphagia, symptomatic oesophageal disease, gastritis, duodenitis, or ulcers—see also under Contra-indications and Side-effects); history (within 1 year) of ulcers, active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract; correct disturbances of calcium and mineral metabolism (e.g. vitamin-D deficiency, hypocalcaemia) before starting and monitor serum-calcium concentration during treatment; consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see Bisphosphonates: Osteonecrosis of the Jaw, p. 394); exclude other causes of osteoporosis; atypical femoral fractures, see MHRA/CHM advice, p. 394; **interactions:** Appendix 1 (bisphosphonates)

Contra-indications abnormalities of oesophagus and other factors which delay emptying (e.g. stricture or achalasia), hypocalcaemia

Renal impairment avoid if estimated glomerular filtration rate is less than 35 mL/minute/1.73 m²

Pregnancy avoid

Breast-feeding no information available

Side-effects oesophageal reactions (see below), abdominal pain and distension, dyspepsia, regurgitation, melaena, diarrhoea or constipation, flatulence, musculoskeletal pain, headache; *rarely* rash, pruritus, erythema, photosensitivity, uveitis, scleritis, transient decrease in serum phosphate; nausea, vomiting, gastritis, peptic ulceration, hypersensitivity reactions (including urticaria and angioedema), atypical femoral fractures with long term use, see MHRA/CHM advice, p. 394; myalgia, malaise, and fever at initiation of treatment; *very rarely* severe skin reactions (including Stevens-Johnson syndrome), osteonecrosis of the jaw (see Bisphosphonates: Osteonecrosis of the Jaw, p. 394)

Oesophageal reactions Severe oesophageal reactions (oesophagitis, oesophageal ulcers, oesophageal stricture and oesophageal erosions) have been reported; patients should be advised to stop taking the tablets and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain

Licensed use not licensed for use in children

Indications and dose

See notes above, specialist use only

Counselling Swallow the tablets whole with a full glass of water on an empty stomach at least 30 minutes before breakfast (and any other oral medication); stand or sit upright for at least 30 minutes and do not lie down until after eating breakfast. Do not take the tablets at bedtime or before rising

Alendronic acid (Non-proprietary) (PoM)

Tablets, alendronic acid (as sodium alendronate) 10 mg, net price 28-tab pack = £1.28; 70 mg, 4-tab pack = 84p. Counselling, administration

Oral solution, sugar-free, alendronic acid (as sodium alendronate) 70 mg/100 mL, net price 4 × 100-mL single-use bottles = £22.80. Counselling, administration

Counselling oral solution intended for single use only; swallow liquid dose with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patients should stand or sit upright for at least 30 minutes after taking the solution

Fosamax® (MSD) (PoM)

Tablets, alendronic acid (as sodium alendronate) 10 mg, net price 28-tab pack = £23.12. Counselling, administration

Fosamax® Once Weekly (MSD) (PoM)

Tablets, alendronic acid (as sodium alendronate) 70 mg, net price 4-tab pack = £22.80. Counselling, administration

atypical femoral fractures, see MHRA/CHM advice, p. 394; **interactions:** Appendix 1 (bisphosphonates)

Skilled tasks Patients should be warned against driving, cycling, or performing skilled tasks immediately after treatment (somnolence or dizziness can occur)

Hepatic impairment use with caution in severe impairment—no information available

Renal impairment monitor renal function in renal disease or predisposition to renal impairment (e.g. in tumour-induced hypercalcaemia)

Pregnancy avoid—toxicity in animal studies

Breast-feeding avoid

Side-effects hypophosphataemia, transient rise in body temperature, fever and influenza-like symptoms (sometimes accompanied by malaise, rigors, fatigue, and flushes); arthralgia, myalgia, bone pain, nausea, vomiting, headache, lymphocytopenia, hypomagnesaemia; *rarely* muscle cramps, atypical femoral fractures, see MHRA/CHM advice, p. 394, anorexia, abdominal pain, diarrhoea, constipation, dyspepsia, agitation, confusion, dizziness, insomnia, somnolence, lethargy, anaemia, leucopenia, hypotension or hypertension, rash, pruritus, symptomatic hypocalcaemia (paraesthesia, tetany), hyperkalaemia or hypokalaemia, hypernatraemia; osteonecrosis of the jaw (see Bisphosphonates: Osteonecrosis of the Jaw, p. 394); isolated cases of seizures, hallucinations, thrombocytopenia, haematuria, acute renal failure, deterioration of renal disease, conjunctivitis and other ocular symptoms; atrial fibrillation, and reactivation of herpes simplex and zoster also reported; also local reactions at injection site

Licensed use not licensed for use in children

Indications and dose

See notes above, specialist use only

Pamidronate disodium (Non-proprietary) (PoM)

Concentrate for intravenous infusion, pamidronate disodium 3 mg/mL, net price 5-mL vial = £13.33, 10-mL vial = £26.66; 6 mg/mL, 10-mL vial = £53.33; 9 mg/mL, 10-mL vial = £80.00; 15 mg/mL, 1-mL vial = £29.83, 2-mL vial = £59.66, 4-mL vial = £119.32, 6-mL vial £170.46

Aredia Dry Powder® (Novartis) (PoM)

Intravenous infusion, powder for reconstitution, pamidronate disodium, net price 15-mg vial = £29.83; 30-mg vial = £59.66; 90-mg vial = £170.45 (all with diluent)

RISEDRONATE SODIUM

Cautions oesophageal abnormalities and other factors which delay transit or emptying (e.g. stricture or achalasia—see also under Side-effects); correct hypocalcaemia before starting, correct other disturbances of bone and mineral metabolism (e.g. Vitamin-D deficiency) at onset of treatment; consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see Bisphosphonates: Osteonecrosis of the Jaw, p. 394); atypical femoral fractures, see MHRA/CHM advice, p. 394; **interactions:** Appendix 1 (bisphosphonates)

Contra-indications hypocalcaemia (see Cautions above)

Renal impairment avoid if estimated glomerular filtration rate is less than 30 mL/minute/1.73 m²

Pregnancy avoid

Breast-feeding avoid

PAMIDRONATE DISODIUM

Pamidronate disodium was formerly called aminohydroxypropylenediphosphonate disodium (APD)

Cautions cardiac disease; previous thyroid surgery (risk of hypocalcaemia); monitor serum electrolytes, calcium, and phosphate—possibility of convulsions due to electrolyte changes; ensure adequate hydration; avoid concurrent use with other bisphosphonates; consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see Bisphosphonates: Osteonecrosis of the Jaw, p. 394);

Side-effects abdominal pain, dyspepsia, nausea, diarrhoea, constipation, headache, musculoskeletal pain; *less commonly* oesophagitis, oesophageal ulcer, dysphagia, gastritis, duodenitis, uveitis; *rarely* glossitis, oesophageal stricture, atypical femoral fractures, see MHRA/CHM advice, p. 394; *also reported* gastro-duodenal ulceration, hepatic disorders, Stevens-Johnson syndrome, toxic epidermal necrolysis, hair loss, cutaneous vasculitis, osteonecrosis of the jaw (see Bisphosphonates: Osteonecrosis of the Jaw, p. 394)

Oesophageal reactions Children and their carers should be advised to stop taking the tablets and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn

Licensed use not licensed for use in children

Indications and dose

See notes above, specialist use only

Counselling Swallow tablets whole with full glass of water; on rising, take on an empty stomach at least 30 minutes before first food or drink of the day or, if taking at any other time of the day, avoid food and drink for at least 2 hours before or after risedronate (particularly avoid calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids); stand or sit upright for at least 30 minutes; do not take tablets at bedtime or before rising

Risedronate Sodium (Non-proprietary) (PoM)

Tablets, risedronate sodium 5 mg, net price 28-tab pack = £13.24; 30 mg, 28-tab pack = £105.70; 35 mg, 4-tab pack = £1.08. Counselling, administration, food, and calcium (see above)

Actonel® (Warner Chilcott) (PoM)

Tablets, f/c, risedronate sodium 5 mg (yellow), net price 28-tab pack = £17.99; 30 mg (white), 28-tab pack = £143.95. Counselling, administration, food, and calcium (see above)

Actonel Once a Week® (Warner Chilcott) (PoM)

Tablets, f/c, orange, risedronate sodium 35 mg, net price 4-tab pack = £19.12. Counselling, administration, food and calcium (see above)

SODIUM CLODRONATE

Cautions monitor renal and hepatic function and white cell count; also monitor serum calcium and phosphate periodically; renal dysfunction reported in patients receiving concomitant NSAIDs; maintain adequate fluid intake during treatment; consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see Bisphosphonates: Osteonecrosis of the Jaw, p. 394); atypical femoral fractures, see MHRA/CHM advice, p. 394; **interactions:** Appendix 1 (bisphosphonates)

Contra-indications acute gastro-intestinal inflammatory conditions

Renal impairment use half normal dose if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy avoid

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, diarrhoea, skin reactions, bronchospasm; *rarely* atypical femoral fractures, see MHRA/CHM advice, p. 394; *very rarely* osteonecrosis of the jaw (see Bisphosphonates: Osteonecrosis of the Jaw, p. 394); *also reported* renal impairment

Licensed use not licensed for use in children

Indications and dose

See notes above, specialist use only

Counselling Avoid food for 2 hours before and 1 hour after oral treatment, particularly calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids; maintain adequate fluid intake

Bonafos® (Bayer) (PoM)

Capsules, yellow, sodium clodronate 400 mg. Net price 120-cap pack = £139.83. Counselling, food and calcium

Tablets, f/c, scored, sodium clodronate 800 mg. Net price 60-tab pack = £146.43. Counselling, food and calcium

Clasteon® (Beacon) (PoM)

Capsules, blue/white, sodium clodronate 400 mg, net price 30-cap pack = £34.96, 120-cap pack = £139.83. Counselling, food and calcium

Tablets, f/c, sodium clodronate 800 mg, net price 60-tab pack = £146.43. Counselling, food and calcium

Loron® (Intrapharm) (PoM)

Loron 520® tablets, f/c, scored, sodium clodronate 520 mg, net price 60-tab pack = £152.59. Label: 10, patient information leaflet, counselling, food and calcium

6.7 Other endocrine drugs

- 6.7.1 Bromocriptine and other dopaminergic drugs
- 6.7.2 Drugs affecting gonadotrophins
- 6.7.3 Metyrapone
- 6.7.4 Somatomedins

6.7.1 Bromocriptine and other dopaminergic drugs

Classification not used in *BNF for Children*.

6.7.2 Drugs affecting gonadotrophins

Classification not used in *BNF for Children*. See section 6.4.2 for use in precocious puberty.

6.7.3 Metyrapone

Metyrapone is a competitive inhibitor of 11 β -hydroxylation in the adrenal cortex; the resulting inhibition of cortisol (and to a lesser extent aldosterone) production leads to an increase in ACTH production which, in turn, leads to increased synthesis and release of cortisol precursors. It is used as a test of anterior pituitary function.

Most types of *Cushing's syndrome* are treated surgically. Metyrapone may be useful to control the symptoms of the disease or to prepare the child for surgery. The dosages used are either low, and tailored to cortisol production, or high, in which case corticosteroid replacement therapy is also needed.

METYRAPONE

Cautions gross hypopituitarism (risk of precipitating acute adrenal failure); hypertension on long-term administration; hypothyroidism (delayed response); many drugs interfere with diagnostic estimation of steroids; avoid in acute porphyria (section 9.8.2)

Skilled tasks Drowsiness may affect the performance of skilled tasks (e.g. driving)

Contra-indications adrenocortical insufficiency (see Cautions)

Hepatic impairment use with caution (delayed response)

Pregnancy avoid (may impair biosynthesis of fetal-placental steroids)

Breast-feeding avoid—no information available

Side-effects occasional nausea, vomiting, dizziness, headache, hypotension, sedation; rarely abdominal pain, allergic skin reactions, hypoadrenalism, hirsutism

Licensed use licensed for use in children

Indications and dose

Differential diagnosis of ACTH-dependent Cushing's syndrome

• By mouth

Child 1 month–18 years 15 mg/kg (or 300 mg/m²) every 4 hours for 6 doses; minimum dose 250 mg every 4 hours, max. 750 mg every 4 hours

Management of Cushing's syndrome

• By mouth

Range 250 mg–6 g daily, adjusted according to cortisol production; see notes above

Metopirone® (HRA Pharma) (PoM)

Capsules, ivory, metyrapone 250 mg, net price 100-cap pack = £363.66. Label: 21, counselling, driving

Side-effects headache, funduscopy for papilloedema recommended if severe or recurrent headache, visual problems, nausea and vomiting occur—if papilloedema confirmed consider benign intracranial hypertension (rare cases reported); cardiomegaly, ventricular hypertrophy, tachycardia; convulsions, sleep apnoea, night terrors, dizziness, nervousness; tonsillar hypertrophy (see Cautions above); hypoglycaemia (especially in first month, and in younger children), hyperglycaemia, gynaecomastia; arthralgia, myalgia; visual disturbance, impaired hearing; antibody formation; injection-site reactions (rotate site)

Indications and dose

Growth failure in children with severe primary insulin-like growth factor-I deficiency

• By subcutaneous injection

Child 2–18 years initially 40 micrograms/kg twice daily for 1 week, if tolerated increase dose in steps of 40 micrograms/kg to max. 120 micrograms/kg twice daily; discontinue if no response within 1 year

Counselling Dose should be administered just before or after food; do not increase dose if a dose is missed

Note Reduce dose if hypoglycaemia occurs despite adequate food intake; withhold injection if patient unable to eat

Increlex® (Ipsen) ▼ (PoM)

Injection, mecamermin 10 mg/mL, net price 4-mL vial = £605.00. Counselling, administration

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

6.7.4 Somatomedins

Somatomedins are a group of polypeptide hormones structurally related to insulin and commonly known as insulin-like growth factors (IGFs). **Mecasermin**, a human insulin-like growth factor-I (rhIGF-I), is the principal mediator of the somatotrophic effects of human growth hormone and is used to treat growth failure in children with severe primary insulin-like growth factor-I deficiency.

MECASERMIN

(Recombinant human insulin-like growth factor-I; rhIGF-I)

Cautions correct hypothyroidism before initiating treatment; diabetes mellitus (adjustment of antidiabetic therapy may be necessary), monitor ECG before and on termination of treatment (and during treatment if ECG abnormal), papilloedema (see under Side-effects), monitor for disorders of the epiphysis of the hip (monitor for limping), monitor for signs of tonsillar hypertrophy (snoring, sleep apnoea, and chronic middle ear effusions)

Contra-indications evidence of tumour activity (discontinue treatment)

Pregnancy avoid unless essential; contraception advised in women of child-bearing potential

Breast-feeding avoid

7 Obstetrics, gynaecology, and urinary-tract disorders

7.1	Drugs used in obstetrics	398
7.2	Treatment of vaginal and vulval conditions	398
7.2.1	Preparations for vaginal and vulval changes	398
7.2.2	Vaginal and vulval infections	398
7.3	Contraceptives	400
7.3.1	Combined hormonal contraceptives	401
7.3.2	Progestogen-only contraceptives	405
7.3.2.1	Oral progestogen-only contraceptives	405
7.3.2.2	Parenteral progestogen-only contraceptives	409
7.3.2.3	Intra-uterine progestogen-only device	410
7.3.3	Spermicidal contraceptives	411
7.3.4	Contraceptive devices	411
7.3.5	Emergency contraception	413
7.4	Drugs for genito-urinary disorders	414
7.4.1	Drugs for urinary retention	414
7.4.2	Drugs for urinary frequency, enuresis, and incontinence	415
7.4.3	Drugs used in urological pain	417
7.4.4	Bladder instillations and urological surgery	417
7.4.5	Drugs for erectile dysfunction	418
7.4.6	Drugs for premature ejaculation	418

7.1 Drugs used in obstetrics

This section is not included in *BNF for Children*. See BNF for management of obstetrics.

For the management of ductus arteriosus, see section 2.14.

7.2 Treatment of vaginal and vulval conditions

7.2.1	Preparations for vaginal and vulval changes
7.2.2	Vaginal and vulval infections

Pre-pubertal girls may be particularly susceptible to vulvovaginitis. Barrier preparations (section 13.2.2) applied after cleansing can be useful when the symptoms are due to non-specific irritation, but systemic drugs are required in the treatment of bacterial infection (section 5.1) or threadworm infestation (section 5.5.1). Intravaginal preparations, particularly those that require the use of an applicator, are not generally suitable for young girls; topical preparations may be useful in some adolescent girls.

In older girls symptoms are often restricted to the vulva, but infections almost invariably involve the vagina, which should also be treated; treatment should be as for adults, see BNF section 7.2.2.

7.2.1 Preparations for vaginal and vulval changes

Topical oestrogen creams containing **estriol** 0.01% (*Gynest*®) are used in the treatment of labial adhesions (for details of preparation, see BNF section 7.2.1); treatment is usually restricted to symptomatic cases. Estriol cream should be applied to the adhesions once or twice daily for 2–6 weeks; adhesions may recur following treatment.

7.2.2 Vaginal and vulval infections

Effective specific treatments are available for the common vaginal infections.

Fungal infections

Vaginal fungal infections are not normally a problem in younger girls but can occur in adolescents. *Candidal vulvitis* can be treated locally with cream, but is almost invariably associated with vaginal infection which should also be treated. *Vaginal candidiasis*, rare in girls before puberty, can be treated with antifungal pessaries or cream inserted high into the vagina (including during menstruation), however, these are not recommended for pre-pubertal girls and treatment with an external cream may be more appropriate. Single-dose intravaginal preparations offer an advantage when compliance is a problem. Local irritation can occur on application of vaginal antifungal products.

Imidazole drugs (clotrimazole, econazole, fenticonazole, and miconazole) are effective against candida in short courses of 1 to 3 days according to the preparation used; treatment can be repeated if initial course fails to control symptoms or if symptoms recur. Vaginal applications may be supplemented with antifungal cream for vulvitis and to treat other superficial sites of infection.

Oral treatment of vaginal infection with fluconazole (section 5.2.1) may be considered for girls post-puberty.

Vulvovaginal candidiasis in pregnancy Vulvovaginal candidiasis is common during pregnancy and can be treated with vaginal application of an imidazole (such as clotrimazole), and a topical imidazole cream for vulvitis. Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection. There is limited absorption of imidazoles from the skin and vagina. Oral antifungal treatment should be avoided during pregnancy.

Recurrent vulvovaginal candidiasis Recurrent vulvovaginal candidiasis is very rare in children, but can occur if there are predisposing factors such as antibacterial therapy, pregnancy, diabetes mellitus, or possibly oral contraceptive use. Reservoirs of infection can also lead to recontamination and should be treated; these include other skin sites such as the digits, nail beds, and umbilicus, as well as the gastro-intestinal tract and the bladder. The sexual partner may also be the source of re-infection and, if symptomatic, should be treated with a topical imidazole cream at the same time.

Treatment against candida may need to be extended for 6 months in recurrent vulvovaginal candidiasis. Some recommended regimens suitable for older children [all unlicensed] include:

- initially, fluconazole (section 5.2.1) 150 mg by mouth every 72 hours for 3 doses, then 150 mg once every week for 6 months;
- initially, intravaginal application of a topical imidazole for 10–14 days, then clotrimazole 500-mg pessary once every week for 6 months.

PREPARATIONS FOR VAGINAL AND VULVAL CANDIDIASIS

Cautions avoid intravaginal preparations (particularly those that require use of an applicator) in young girls who are not sexually active, unless there is no alternative; **interactions:** Appendix 1 (miconazole)

Pregnancy see notes above

Side-effects occasional local irritation

Licensed use consult product literature for individual preparations

Indications and dose

See notes above and under preparations below

Clotrimazole (Non-proprietary)

Cream (topical), clotrimazole 1%, net price 20 g = £1.26, 50 g = £3.15

Condoms effect on latex condoms and diaphragms not yet known

Dose

Apply to anogenital area 2–3 times daily

Pessary, clotrimazole 500 mg, net price 1 pessary with applicator = £3.12

Dose

Insert 1 pessary at night as a single dose; can be repeated once if necessary

Canesten® (Bayer Consumer Care)

Cream (topical), clotrimazole 1%, net price 20 g = £2.14; 50 g = £3.50

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose

Apply to anogenital area 2–3 times daily

Thrush Cream (topical), clotrimazole 2%, net price 20 g = £4.46

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose

Apply to anogenital area 2–3 times daily

Intravaginal cream (10% VC®) (POM), clotrimazole 10%, net price 5-g applicator pack = £4.50

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose

Insert 5 g at night as a single dose; may be repeated once if necessary

Note Brands for sale to the public include *Canesten® Internal Cream*

Cream Combi, clotrimazole 10% vaginal cream and 2% topical cream, net price 5-g vaginal cream (with applicator) and 10-g topical cream = £8.21

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose

See under individual components

Pessaries, clotrimazole 200 mg, net price 3 pessaries with applicator = £3.10

Condoms damages latex condoms and diaphragms

Dose

Insert 200 mg for 3 nights; course may be repeated once if necessary

Pessary, clotrimazole 500 mg, net price 1 pessary with applicator = £2.00

Excipients none as listed in section 13.1.3

Condoms damages latex condoms and diaphragms

Dose

Insert 1 pessary at night as a single dose; may be repeated once if necessary

Pessary Combi, clotrimazole 500-mg pessary and cream (topical) 2%, net price 1 pessary and 10-g cream = £8.21

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose

See under individual components

Soft Gel Pessary, clotrimazole 500 mg, net price 1 pessary with applicator = £6.41

Condoms damages latex condoms and diaphragms

Dose

Insert 1 pessary at night as a single dose; may be repeated once if necessary

Soft Gel Pessary Combi, clotrimazole 500-mg soft gel pessary and cream (topical) 2%, net price 1 pessary and 10-g cream = £5.73

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose

See under individual components

Gyno-Daktarin® (Janssen) **[PoM]**
Ovule (= vaginal capsule) (*Gyno-Daktarin 1®*), miconazole nitrate 1.2 g in a fatty basis, net price 1 ovule = £2.94
Excipients include hydroxybenzoates (parabens)
Condoms damages latex condoms and diaphragms
Dose

Insert 1 ovule at night as a single dose; can be repeated once if necessary

Gyno-Pevaryl® (Janssen) **[PoM]**
Pessaries, econazole nitrate 150 mg, net price 3 pessaries = £4.17
Excipients none as listed in section 13.1.3
Condoms damages latex condoms and diaphragms
Dose

Insert 1 pessary for 3 nights; course can be repeated once if necessary

Pessary (*Gyno-Pevaryl 1®*), econazole nitrate 150 mg, formulated for single-dose therapy, net price 1 pessary with applicator = £3.69
Excipients none as listed in section 13.1.3
Condoms damages latex condoms and diaphragms
Dose

Insert 1 pessary at night as a single dose; can be repeated once if necessary

Gynoxin® (Recordati) **[PoM]**
Intravaginal cream, fenticonazole nitrate 2%, net price 30 g with applicator = £3.74
Excipients include cetyl alcohol, hydrogenated wool fat, propylene glycol
Condoms damages latex condoms and diaphragms
Dose

Insert 5-g applicatorful intravaginally twice daily for 3 days

Vaginal capsule, fenticonazole nitrate 200 mg, net price 3 vaginal capsules = £2.42
Excipients include hydroxybenzoates (parabens)
Condoms damages latex condoms and diaphragms
Dose

Insert 1 vaginal capsule at night for 3 nights

Vaginal capsule, fenticonazole nitrate 600 mg, net price 1 vaginal capsule = £2.62
Excipients include hydroxybenzoates (parabens)
Condoms damages latex condoms and diaphragms
Dose

Insert 1 vaginal capsule at night as a single dose

Other infections

Trichomonas infections commonly involve the lower urinary tract as well as the genital system and need systemic treatment with metronidazole (section 5.1.11) or tinidazole (section 5.4.2).

Bacterial infections with Gram-negative organisms are particularly common in association with gynaecological operations and trauma. Metronidazole is effective against certain Gram-negative organisms, especially *Bacteroides* spp. and can be used prophylactically in gynaecological surgery.

Clindamycin cream and metronidazole gel are indicated for bacterial vaginosis.

The antiviral drugs aciclovir, famciclovir, and valaciclovir can be used in the treatment of genital infection due

to *herpes simplex virus*, the HSV type 2 being a major cause of genital ulceration. They have a beneficial effect on virus shedding and healing, generally giving relief from pain and other symptoms. See section 5.3 for systemic preparations, and section 13.10.3 for topical preparations.

PREPARATIONS FOR OTHER VAGINAL INFECTIONS

Cautions avoid intravaginal preparations (particularly those that require the use of an applicator) in young girls who are not sexually active, unless there is no alternative.

Balance Activ Rx® (BBI Healthcare)
Vaginal gel, lactic acid 4.9%, glycogen 0.1%, net price 7 x 5 mL-tube = £5.25
Excipients include propylene glycol
Dose

Prevention of bacterial vaginosis
 Insert contents of 1 tube once or twice weekly

Dalacin® (Pharmacia) **[PoM]**
Cream, clindamycin 2% (as phosphate), net price 40-g pack with 7 applicators = £10.86
Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates, propylene glycol
Condoms damages latex condoms and diaphragms
Side-effects irritation, cervicitis and vaginitis; poorly absorbed into the blood—low risk of systemic effects, see section 5.1.6

Licensed use not licensed for use in children
Dose
Bacterial vaginosis
 Insert 5-g applicatorful at night for 3–7 nights

Zidoval® (Meda) **[PoM]**
Vaginal gel, metronidazole 0.75%, net price 40-g pack with 5 applicators = £4.31
Excipients include disodium edetate, hydroxybenzoates (parabens), propylene glycol
Side-effects local effects including irritation, candidiasis, abnormal discharge, pelvic discomfort
Licensed use not licensed for use in children under 18 years
Note Not recommended during menstruation; some absorption may occur, see section 5.1.11 for systemic effects
Dose

Bacterial vaginosis
 Insert 5-g applicatorful at night for 5 nights

7.3 Contraceptives

- 7.3.1 Combined hormonal contraceptives
- 7.3.2 Progestogen-only contraceptives
- 7.3.3 Spermicidal contraceptives
- 7.3.4 Contraceptive devices
- 7.3.5 Emergency contraception

The Fraser Guidelines¹ should be followed when prescribing contraception for women under 16 years. The UK Medical Eligibility Criteria for Contraceptive Use

1. See Department of Health Guidance (July 2004): Best practice guidance for doctors and other health professionals on the provision of advice and treatment to young people under 16 on contraception, sexual and reproductive health. Available at tinyurl.com/bpg16

(available at www.fsrh.org) is published by the Faculty of Sexual and Reproductive Healthcare; it categorises the risks of using contraceptive methods with pre-existing medical conditions.

Hormonal contraception is the most effective method of fertility control, but can have major and minor side-effects, especially for certain groups of women. Hormonal contraception should only be used by adolescents after menarche.

Intra-uterine devices are a highly effective method of contraception but may produce undesirable local side-effects. They may be used in women of all ages irrespective of parity but are less appropriate for those with an increased risk of pelvic inflammatory disease.

Barrier methods alone (condoms, diaphragms, and caps) are less effective but can be reliable for well-motivated couples if used in conjunction with a **spermicide**. Occasionally sensitivity reactions occur. A female condom (*Femidom*®) is also available; it is pre-lubricated but does not contain a spermicide.

7.3.1 Combined hormonal contraceptives

Oral contraceptives containing an oestrogen and a progestogen ('combined oral contraceptives') are effective preparations for general use. Advantages of combined oral contraceptives include:

- reliable and reversible;
- reduced dysmenorrhoea and menorrhagia;
- reduced incidence of premenstrual tension;
- reduced risk of symptomatic fibroids and functional ovarian cysts;
- less benign breast disease;
- reduced risk of ovarian and endometrial cancer;
- reduced risk of pelvic inflammatory disease.

Combined oral contraceptives containing a fixed amount of an oestrogen and a progestogen in each active tablet are termed 'monophasic'; those with varying amounts of the two hormones are termed 'phasic'. A transdermal patch and a vaginal ring, both containing an oestrogen with a progestogen, are also available.

Choice The majority of combined oral contraceptives contain ethinylestradiol as the oestrogen component; mestranol and estradiol valerate are also used. The ethinylestradiol content of combined oral contraceptives ranges from 20 to 40 micrograms. Generally a preparation with the lowest oestrogen and progestogen content which gives good cycle control and minimal side-effects in the individual woman is chosen.

- **Low strength preparations** (containing ethinylestradiol 20 micrograms) are particularly appropriate for women with risk factors for circulatory disease, provided a combined oral contraceptive is otherwise suitable.
- **Standard strength preparations** (containing ethinylestradiol 30 or 35 micrograms or in 30–40 microgram phased preparations) are appropriate for standard use—but see Risk of Venous Thromboembolism below. Phased preparations are generally reserved for women who *either* do not have withdrawal bleeding or who have breakthrough bleeding with monophasic products.

The progestogens desogestrel, drospirenone, and gestodene (in combination with ethinylestradiol) may be

considered for women who have side-effects (such as acne, headache, depression, breast symptoms, and breakthrough bleeding) with other progestogens. Drospirenone, a derivative of spironolactone, has anti-androgenic and anti-mineralocorticoid activity; it should be used with care if an increased plasma-potassium concentration might be hazardous.

The progestogen norelgestromin is combined with ethinylestradiol in a transdermal patch (*Evra*®).

The vaginal contraceptive ring contains the progestogen etonogestrel combined with ethinylestradiol (*NuvaRing*®).

Risk of venous thromboembolism There is an increased risk of venous thromboembolic disease in users of combined hormonal contraceptives particularly during the first year and possibly after restarting combined hormonal contraceptives following a break of four weeks or more. This risk is considerably smaller than that associated with pregnancy (about 60 cases of venous thromboembolic disease per 100 000 pregnancies). In all cases the risk of venous thromboembolism increases with age and in the presence of other risk factors, such as obesity. The risk also varies depending on the type of progestogen, see Combined Hormonal Contraception and Risk of Venous Thromboembolism table below for details.

Provided that women are informed of the relative risks of venous thromboembolism and accept them, the choice of oral contraceptive is for the woman together with the prescriber jointly to make in light of her individual medical history and any contra-indications.

Combined Hormonal Contraception and Risk of Venous Thromboembolism

Progestogen in Combined Hormonal Contraceptive	Estimated incidence per 10 000 women per year of use
Non-pregnant, not using combined hormonal contraception	2
Levonorgestrel ¹	5–7
Norgestimate ¹	
Norethisterone ¹	
Etonogestrel ¹	6–12
Norelgestromin ¹	
Gestodene ¹	9–12
Desogestrel ¹	
Drospirenone ¹	
Dienogest ²	Not known—insufficient data
Nomegestrol acetate ²	

1. Combined with ethinylestradiol

2. Combined with estradiol

Combined hormonal contraceptives also slightly increase the risk of arterial thromboembolism; however, there is no evidence to suggest that this risk varies between different preparations.

Travel Women taking oral contraceptives or using the patch or vaginal ring are at an increased risk of deep-vein thrombosis during travel involving long periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery.

Missed pill The critical time for loss of contraceptive protection is when a pill is omitted at the *beginning* or *end* of a cycle (which lengthens the pill-free interval).

If a woman forgets to take a pill, it should be taken as soon as she remembers, and the next one taken at the normal time (even if this means taking 2 pills together). A missed pill is one that is 24 or more hours late; for women taking *Qlaira*®, see below. If a woman misses only one pill, she should take an active pill as soon as she remembers and then resume normal pill-taking. No additional precautions are necessary.

If a woman misses 2 or more pills (especially from the first 7 in a packet), she may not be protected. She should take an active pill as soon as she remembers and then resume normal pill-taking. In addition, she must either abstain from sex or use an additional method of contraception such as a condom for the next 7 days. If these 7 days run beyond the end of the packet, the next packet should be started at once, omitting the pill-free interval (or, in the case of *everyday* (ED) pills, omitting the 7 inactive tablets).

A missed pill for a woman taking *Qlaira*® is one that is 12 hours or more late; for information on how to manage missed pills in women taking *Qlaira*®, refer to product literature.

Emergency contraception (section 7.3.5) is recommended if 2 or more combined oral contraceptive tablets are missed from the first 7 tablets in a packet and unprotected intercourse has occurred since finishing the last packet.

Delayed application or detached patch If a patch is partly detached for less than 24 hours, reapply to the same site or replace with a new patch immediately; no additional contraception is needed and the next patch should be applied on the usual 'change day'. If a patch remains detached for more than 24 hours or if the user is not aware when the patch became detached, then stop the current contraceptive cycle and start a new cycle by applying a new patch, giving a new 'Day 1'; an additional non-hormonal contraceptive must be used concurrently for the first 7 days of the new cycle.

If application of a new patch at the start of a new cycle is delayed, contraceptive protection is lost. A new patch should be applied as soon as remembered giving a new 'Day 1'; additional non-hormonal methods of contraception should be used for the first 7 days of the new cycle. If application of a patch in the middle of the cycle is delayed (i.e. the patch is not changed on day 8 or day 15):

- for up to 48 hours, apply a new patch immediately; next patch 'change day' remains the same and no additional contraception is required;
- for more than 48 hours, contraceptive protection may have been lost. Stop the current cycle and start a new 4-week cycle immediately by applying a new patch giving a new 'Day 1'; additional non-hormonal contraception should be used for the first 7 days of the new cycle.

If the patch is not removed at the end of the cycle (day 22), remove it as soon as possible and start the next cycle on the usual 'change day', the day after day 28; no additional contraception is required.

Expulsion, delayed insertion or removal, or broken vaginal ring If the vaginal ring is expelled for *less than 3 hours*, rinse the ring with cool water and reinsert immediately; no additional contraception is needed.

If the ring remains outside the vagina for *more than 3 hours* or if the user does not know when the ring was expelled, contraceptive protection may be reduced:

- if ring expelled during week 1 or 2 of cycle, rinse ring with cool water and reinsert; use additional precautions (barrier methods) for next 7 days;
- if ring expelled during week 3 of cycle, either insert a new ring to start a new cycle or allow a withdrawal bleed and insert a new ring no later than 7 days after ring was expelled; latter option only available if ring was used continuously for at least 7 days before expulsion.

If insertion of a new ring at the start of a new cycle is delayed, contraceptive protection is lost. A new ring should be inserted as soon as possible; additional precautions (barrier methods) should be used for the first 7 days of the new cycle. If intercourse occurred during the extended ring-free interval, pregnancy should be considered.

No additional contraception is required if the removal of the ring is delayed by up to 1 week (4 weeks of continuous use). The 7-day ring-free interval should be observed and subsequently a new ring should be inserted. Contraceptive protection may be reduced with continuous use of the ring for more than 4 weeks—pregnancy should be ruled out before inserting a new ring.

If the ring breaks during use, remove it and insert a new ring immediately; additional precautions (barrier methods) should be used for the first 7 days of the new cycle.

Diarrhoea and vomiting Vomiting and persistent, severe diarrhoea can interfere with the absorption of combined oral contraceptives. If vomiting occurs within 2 hours of taking a combined oral contraceptive another pill should be taken as soon as possible. In cases of persistent vomiting or severe diarrhoea lasting more than 24 hours, additional precautions should be used during and for 7 days (9 days for *Qlaira*®) after recovery (see also under Missed pill, above). If the vomiting and diarrhoea occurs during the last 7 tablets, the next pill-free interval should be omitted (in the case of ED tablets the inactive ones should be omitted).

Interactions The effectiveness of *combined* oral contraceptives, *progestogen-only* oral contraceptives (section 7.3.2.1), contraceptive patches, and vaginal rings can be considerably reduced by interaction with drugs that induce hepatic enzyme activity (e.g. carbamazepine, nevirapine, oxcarbazepine, phenytoin, phenobarbital, primidone, ritonavir, St John's Wort, topiramate, and, above all, rifabutin and rifampicin). A condom together with a long-acting method, such as an injectable contraceptive, may be more suitable for patients with HIV infection or at risk of HIV infection; advice on the possibility of interaction with anti-retroviral drugs should be sought from HIV specialists.

Women taking combined hormonal contraceptives who require enzyme-inducing drugs should be advised to change to a contraceptive method that is unaffected by enzyme-inducers (e.g. some parenteral progestogen-only contraceptives (p. 409), intra-uterine devices) for

the duration of treatment and for 4 weeks after stopping. If a change in contraceptive method is undesirable or inappropriate the following options should be discussed:

- For a *short course (2 months or less) of an enzyme-inducing drug*, continue with a combined oral contraceptive providing ethinylestradiol 30 micrograms or more daily and use a 'tricycling' regimen (i.e. taking 3 packets of monophasic tablets without a break followed by a shortened tablet-free interval of 4 days [unlicensed use]). Additional contraceptive precautions should also be used whilst taking the enzyme-inducing drug and for 4 weeks after stopping. Another option (except for rifampicin or rifabutin—see below) is to follow the advice for long-term courses, below.

For women using combined hormonal contraceptive patches or vaginal rings, additional contraceptive precautions are also required whilst taking the enzyme-inducing drug and for 4 weeks after stopping. If concomitant administration runs beyond the 3 weeks of patch or vaginal ring use, a new treatment cycle should be started immediately, without a patch-free or ring-free break.

- For a *long-term course (over 2 months) of an enzyme-inducing drug* (except rifampicin or rifabutin—see below), adjust the dose of combined oral contraceptive to provide ethinylestradiol 50 micrograms or more daily [unlicensed use] and use a 'tricycling' regimen (as above); continue for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping.

If breakthrough bleeding occurs (and all other causes are ruled out) it is recommended that the dose of ethinylestradiol is increased by increments of 10 micrograms up to a maximum of 70 micrograms daily [unlicensed use], or to use additional precautions, or to change to a method unaffected by enzyme-inducing drugs.

Contraceptive patches and vaginal rings are not recommended for women taking enzyme-inducing drugs over a long period.

- For a *long-term course (over 2 months) of rifampicin or rifabutin*, an alternative method of contraception (such as an IUD) is **always** recommended because they are such potent enzyme-inducing drugs; the alternative method of contraception should be continued for 4 weeks after stopping the enzyme-inducing drug.

For information on interactions of oral progestogen-only contraceptives, see also p. 408; for information on interactions of parenteral progestogen-only contraceptives, see also p. 409; for information on interactions of the intra-uterine progestogen-only device, see also p. 410; for information on interactions of hormonal emergency contraception, see also p. 414

Antibacterials that do not induce liver enzymes

Latest recommendations are that no additional contraceptive precautions are required when combined oral contraceptives are used with antibacterials that do not induce liver enzymes (e.g. ampicillin, doxycycline), unless diarrhoea or vomiting occur (see above). These recommendations should be discussed with the woman, who should also be advised that guidance in patient information leaflets may differ.

It is also currently recommended that no additional contraceptive precautions are required when contraceptive patches or vaginal rings are used with antibacterials that do not induce liver enzymes. There have been concerns that some antibacterials that do not induce liver enzymes reduce the efficacy of combined oral contraceptives by impairing the bacterial flora responsible for recycling ethinylestradiol from the large bowel; however, there is a lack of evidence to support this interaction.

Surgery Oestrogen-containing contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilisation of a lower limb; they should normally be recommenced at the first menses occurring at least 2 weeks after full mobilisation. A progestogen-only contraceptive may be offered as an alternative and the oestrogen-containing contraceptive restarted after mobilisation, as above. When discontinuation of an oestrogen-containing contraceptive is not possible, e.g. after trauma or if a patient admitted for an elective procedure is still on an oestrogen-containing contraceptive, thromboprophylaxis (with unfractionated or low molecular weight heparin and graduated compression hosiery) is advised. These recommendations do not apply to minor surgery with short duration of anaesthesia, e.g. laparoscopic sterilisation or tooth extraction, or to women using oestrogen-free hormonal contraceptives.

Reason to stop immediately Combined hormonal contraceptives should be stopped (pending investigation and treatment), if any of the following occur:

- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- serious neurological effects including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphasia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- hepatitis, jaundice, liver enlargement;
- very high blood pressure;
- prolonged immobility after surgery or leg injury;
- detection of a risk factor which contra-indicates treatment (see Cautions and Contra-indications under Combined Hormonal Contraceptives below).

COMBINED HORMONAL CONTRACEPTIVES

Cautions see notes above; also risk factors for venous thromboembolism (see below and also notes above), arterial disease and migraine, see below; personal or family history of hypertriglyceridaemia (increased risk of pancreatitis); hyperprolactinaemia (seek specialist advice); history of severe depression especially if induced by hormonal contraceptive; undiagnosed breast mass; gene mutations associated with breast cancer (e.g. BRCA 1); sickle-cell disease; inflamm-

atory bowel disease including Crohn's disease; reduced efficacy of contraceptive patch in women with body-weight ≥ 90 kg; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration) —seek specialist advice; **interactions:** see above and Appendix 1 (oestrogens, progestogens)

Risk factors for venous thromboembolism See also notes above. Use with **caution** if any of the following factors present but **avoid** if two or more factors present:

- *family history of venous thromboembolism* in first-degree relative aged under 45 years (avoid contraceptive containing desogestrel or gestodene, or avoid if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));
- *obesity*—caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative;
- *long-term immobilisation* e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast);
- *history of superficial thrombophlebitis*;
- *smoking*.

Risk factors for arterial disease Use with **caution** if any one of the following factors present but **avoid** if two or more factors present:

- *family history of arterial disease* in first degree relative aged under 45 years (avoid if atherogenic lipid profile);
- *diabetes mellitus* (avoid if diabetes complications present);
- *hypertension* (avoid if blood pressure very high);
- *smoking* (avoid if smoking 40 or more cigarettes daily);
- *obesity*—caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative;
- *migraine without aura* (avoid if *migraine with aura* (focal symptoms), or severe migraine frequently lasting over 72 hours despite treatment, or migraine treated with ergot derivatives).

Migraine Women should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour—see also Reason to stop immediately in notes above)

Contra-indications see notes above; also personal history of venous or arterial thrombosis, severe or multiple risk factors for arterial disease or for venous thromboembolism (see above), heart disease associated with pulmonary hypertension or risk of embolus; sclerosing treatment for varicose veins; migraine with aura (see also above); transient cerebral ischaemic attacks without headaches; systemic lupus erythematosus; acute porphyria (section 9.8.2); gallstones; history of haemolytic uraemic syndrome or history during pregnancy of pruritus, cholestatic jaundice, chorea, pemphigoid gestationis; history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable; undiagnosed vaginal bleeding

Hepatic impairment avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours

Pregnancy not known to be harmful

Breast-feeding avoid until weaning or for 6 months after birth (adverse effects on lactation)

Side-effects see notes above; also nausea, vomiting, abdominal cramps, liver impairment, hepatic tumours; fluid retention, thrombosis (more common

when factor V Leiden present or in blood groups A, B, and AB; see also notes above), hypertension, changes in lipid metabolism; headache, depression, chorea, nervousness, irritability; changes in libido, breast tenderness, enlargement, and secretion; reduced menstrual loss, 'spotting' in early cycles, absence of withdrawal bleeding, amenorrhoea after discontinuation, changes in vaginal discharge, cervical erosion; contact lenses may irritate, visual disturbances; leg cramps; skin reactions, chloasma, photosensitivity; rarely gallstones and systemic lupus erythematosus

Breast cancer There is a small increase in the risk of having breast cancer diagnosed in women taking the combined oral contraceptive pill; this relative risk may be due to an earlier diagnosis. In users of combined oral contraceptive pills the cancers are more likely to be localised to the breast. The most important factor for diagnosing breast cancer appears to be the age at which the contraceptive is stopped rather than the duration of use; any increase in the rate of diagnosis disappears gradually during the 10 years after stopping and disappears by 10 years

Cervical cancer Use of combined oral contraceptives for 5 years or longer is associated with a small increased risk of cervical cancer; the risk diminishes after stopping and disappears by about 10 years. The risk of cervical cancer with transdermal patches and vaginal rings is not yet known

Note The possible small increase in the risk of breast cancer and cervical cancer should be weighed against the protective effect against cancers of the ovary and endometrium

Licensed use consult product literature for the licensing status of individual preparations

Indications and dose

Contraception, menstrual symptoms (section 6.4.1.2)

• By mouth

Each tablet should be taken at approximately same time each day; if delayed, contraceptive protection may be lost (see Missed Pill, above)

21-day combined (monophasic) preparations, 1 tablet daily for 21 days; subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs); if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days

Every day (ED) combined (monophasic) preparations, 1 *active* tablet daily for 21 days, followed by 1 *inactive* tablet daily for 7 days (see also Combined Oral Contraceptives table, below); subsequent courses repeated without interval (withdrawal bleeding occurs when *inactive* tablets being taken); if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days

Phasic preparations, see Combined Oral Contraceptives table, below

Changing to combined preparation containing different progestogen If previous contraceptive used correctly, or pregnancy can reasonably be excluded, start the first *active* tablet of new brand immediately

Changing to Qlaira®: start the first *active* Qlaira® tablet on the day after taking the last *active* tablet of the previous brand

Changing from Qlaira®: start the new brand after taking the last *active* Qlaira® tablet; if the *inactive* tablets are taken before starting new brand, additional precautions (barrier methods) should be used during first 7 days of taking the new brand

Changing from progestogen-only tablet If previous contraceptive used correctly, or pregnancy can reasonably be excluded, start new brand immediately, additional precautions (barrier methods) necessary for first 7 days

Changing to *Qlaira*®, start any day, additional precautions (barrier methods) necessary for first 9 days

Secondary amenorrhoea (exclude pregnancy) Start any day, additional precautions (barrier methods) necessary during first 7 days (9 days for *Qlaira*®)

After childbirth (not breast-feeding) Start 3 weeks after birth (increased risk of thrombosis if started earlier); later than 3 weeks postpartum additional precautions (barrier methods) necessary for first 7 days (9 days for *Qlaira*®)

After abortion or miscarriage Start same day

• By transdermal application

Apply first patch on day 1 of cycle, change patch on days 8 and 15; remove third patch on day 22 and apply new patch after 7-day patch-free interval to start subsequent contraceptive cycle

Note If first patch applied later than day 1, additional precautions (barrier methods) should be used for the next 7 days

Changing from combined oral contraception Apply patch on the first day of withdrawal bleeding; if no withdrawal bleeding within 5 days of taking last active tablet, rule out pregnancy before applying first patch. Unless patch is applied on first day of withdrawal bleeding, additional precautions (barrier methods) should be used concurrently for first 7 days

Changing from progestogen-only method From an implant, apply first patch on the day implant removed; from an injection, apply first patch when next injection due; from oral progestogen, first patch may be applied on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days

After childbirth (not breast-feeding) Start 4 weeks after birth; if started later than 4 weeks after birth additional precautions (barrier methods) should be used for first 7 days

After abortion or miscarriage Before 20 weeks' gestation start immediately; no additional contraception required if started immediately. After 20 weeks' gestation start on day 21 after abortion or on the first day of first spontaneous menstruation; additional precautions (barrier methods) should be used for first 7 days after applying the patch

• By vagina

Insert ring into vagina on day 1 of cycle and leave in for 3 weeks; remove ring on day 22; subsequent courses repeated after 7-day ring-free interval (during which withdrawal bleeding occurs)

Note If first ring inserted later than day 1, additional precautions (barrier methods) should be used for the next 7 days

Changing from combined hormonal contraception Insert ring at the latest on the day after the usual tablet-free, patch-free, or inactive-tablet interval. If previous contraceptive used correctly, or pregnancy can reasonably be excluded, can switch to ring on any day of cycle

Changing from progestogen-only method From an implant or intra-uterine progestogen-only device, insert ring on the day implant or intra-uterine progestogen-only device removed; from an injection, insert ring when injection next due; from oral preparation, first ring may be inserted on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days

After first trimester abortion Start immediately

After childbirth (not breast-feeding) or second trimester abortion Start 4 weeks after birth or abortion; if started later than 4 weeks after birth or abortion additional precautions (barrier methods) should be used for first 7 days

Oral (low and standard strength)

For information on these preparations, see Combined Oral Contraceptives table, p. 406

Transdermal (standard strength)

■ Ethinylestradiol with Norelgestromin

See Risk of Venous Thromboembolism (in notes above) before prescribing

Evra® (Janssen) [PoM]

Patches, self-adhesive (releasing ethinylestradiol approx. 33.9 micrograms/24 hours and norelgestromin approx. 203 micrograms/24 hours); net price 9-patch pack = £19.51. Counselling, administration **Dose**

1 patch to be applied once weekly for three weeks, followed by a 7-day patch-free interval; subsequent courses repeated after 7-day patch-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Note Adhesives or bandages should not be used to hold patch in place. If patch no longer sticky do not reapply but use a new patch.

The *Scottish Medicines Consortium* has advised (September 2003) that *Evra*® patches should be restricted for use in women who are likely to comply poorly with combined oral contraceptives

Vaginal (low strength)

■ Ethinylestradiol with Etonogestrel

See Risk of Venous Thromboembolism (in notes above) before prescribing

NuvaRing® (MSD) ▼ [PoM]

Vaginal ring, releasing ethinylestradiol approx. 15 micrograms/24 hours and etonogestrel approx. 120 micrograms/24 hours, net price 3-ring pack = £27.00. Counselling, administration **Dose**

1 ring to be inserted into the vagina for 3 weeks, removed on day 22; subsequent courses repeated after 7-day ring-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Counselling The presence of the ring should be checked regularly. In case of expulsion see Expulsion, Delayed Insertion or Removal, or Broken Vaginal Ring, p. 402

7.3.2 Progestogen-only contraceptives

7.3.2.1 Oral progestogen-only contraceptives

7.3.2.2 Parenteral progestogen-only contraceptives

7.3.2.3 Intra-uterine progestogen-only device

7.3.2.1 Oral progestogen-only contraceptives

Oral progestogen-only preparations alter cervical mucus to prevent sperm penetration and may inhibit ovulation in some women; oral desogestrel-only preparations consistently inhibit ovulation and this is their primary mechanism of action. There is insufficient clinical trial evidence to compare the efficacy of oral progestogen-only contraceptives with each other or with combined hormonal contraceptives. Progestogen-only

Combined Oral Contraceptives

See Risk of Venous Thromboembolism (in notes above) before prescribing

Type of preparation	Oestrogen content	Progestogen content	Tablets per cycle	Brand	Price, 3-cycle pack (unless stated)	Manufacturer
¹ Monophasic low strength (21-day preparations)	Ethinylestradiol 20 micrograms	Desogestrel 150 micrograms	21	Gedarel [®] 20/150	£5.98	Consilient
				Mercilon [®]	£7.97	MSD
		Gestodene 75 micrograms	21	Femodette [®]	£8.85	Bayer
				Millinette [®] 20/75	£6.37	Consilient
		Norethisterone acetate 1 mg	21	Sunya 20/75 [®] Loestrin 20 [®]	£6.62 £2.70	Stragen Galen
¹ Monophasic standard strength (21-day preparations)	Ethinylestradiol 30 micrograms	Desogestrel 150 micrograms	21	Gedarel [®] 30/150	£4.93	Consilient
				Marvelon [®]	£6.45	MSD
		Drospirenone 3 mg	21	² Yasmin [®]	£14.70	Bayer
				Femodene [®]	£6.73	Bayer
		Gestodene 75 micrograms	21	Katya 30/75 [®]	£5.03	Stragen
				Millinette [®] 30/75	£4.85	Consilient
	Ethinylestradiol 35 micrograms	Levonorgestrel 150 micrograms	21	Levest [®]	£1.80	Morningside
				Microgynon 30 [®]	£2.82	Bayer
				Ovranette [®]	£2.20	Pfizer
				Rigevidon [®]	£1.89	Consilient
		Norethisterone acetate 1.5 mg	21	Loestrin 30 [®]	£3.90	Galen
	Mestranol 50 micrograms	Norgestimate 250 micrograms	21	Cilest [®]	£7.16	Janssen
				Brevinor [®]	£1.99	Pharmacia
				Ovysmen [®]	£1.49	Janssen
	Mestranol 50 micrograms	Norethisterone 1 mg	21	Norimin [®]	£2.28	Pharmacia
				Norinyl-1 [®]	£2.19	Pharmacia
³ Monophasic standard strength (28-day 'Every day' preparations)	Ethinylestradiol 30 micrograms	Gestodene 75 micrograms	21 active	Femodene [®] ED	£7.10	Bayer
			7 inactive			
	Ethinylestradiol 30 micrograms	Levonorgestrel 150 micrograms	21 active	Microgynon 30 ED [®]	£2.99	Bayer
			7 inactive			

1. Dose 1 tablet daily for 21 days starting on day 1–5 of cycle (if reasonably certain woman is not pregnant, first course can be started on any day of cycle); subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting and changing routines see under Indications and Dose above
2. Caution use with care if increased plasma-potassium concentration might be hazardous; renal impairment avoid if eGFR less than 30 mL/minute/1.73 m²
3. Dose 1 tablet daily for 28 days starting on day 1–5 of cycle with first active tablet (withdrawal bleeding occurs when inactive tablets being taken) (if reasonably certain woman is not pregnant, first course can be started on any day of cycle); subsequent courses repeated without interval; for starting and changing routines see under Indications and Dose above

Combined Oral Contraceptives (continued)

See Risk of Venous Thromboembolism (in notes above) before prescribing

Type of preparation	Oestrogen content	Progestogen content	Tablets per cycle	Brand	Price, 3-cycle pack (unless stated)	Manufacturer
¹ Phasic standard strength (21-day preparations)	Ethinylestradiol 30 micrograms	Gestodene 50 micrograms	6	Triadene®	£10.40	Bayer
	Ethinylestradiol 40 micrograms	Gestodene 70 micrograms	5			
	Ethinylestradiol 30 micrograms	Gestodene 100 micrograms	10			
	Ethinylestradiol 30 micrograms	Levonorgestrel 50 micrograms	6	Logynon®	£3.82	Bayer
	Ethinylestradiol 40 micrograms	Levonorgestrel 75 micrograms	5			
	Ethinylestradiol 30 micrograms	Levonorgestrel 125 micrograms	10	TriRegol®	£2.87	Consilient
	Ethinylestradiol 35 micrograms	Norethisterone 500 micrograms	7	BiNovum®	£2.49	Janssen
	Ethinylestradiol 35 micrograms	Norethisterone 1 mg	14			
	Ethinylestradiol 35 micrograms	Norethisterone 500 micrograms	7	Synphase®	1-cycle pack = £1.20	Pharmacia
	Ethinylestradiol 35 micrograms	Norethisterone 1 mg	9			
	Ethinylestradiol 35 micrograms	Norethisterone 500 micrograms	5			
	Ethinylestradiol 35 micrograms	Norethisterone 500 micrograms	7	TriNovum®	£3.46	Janssen
	Ethinylestradiol 35 micrograms	Norethisterone 750 micrograms	7			
	Ethinylestradiol 35 micrograms	Norethisterone 1 mg	7			
² Phasic standard strength (28-day 'Every day' preparation)	Ethinylestradiol 30 micrograms	Levonorgestrel 50 micrograms	6 active	Logynon ED®	£4.00	Bayer
	Ethinylestradiol 40 micrograms	Levonorgestrel 75 micrograms	5 active			
	Ethinylestradiol 30 micrograms	Levonorgestrel 125 micrograms	10 active			
			7 inactive			
³ Phasic (28-day 'Every day' preparation)	Estradiol valerate 3 mg	Dienogest 2 mg	2 active	Qlaira®	£25.18	Bayer
	Estradiol valerate 2 mg		5 active			
	Estradiol valerate 2 mg	Dienogest 3 mg	17 active			
	Estradiol valerate 1 mg		2 active			
			2 inactive			

- ¹ Dose 1 tablet daily for 21 days starting on day 1–5 of cycle (if reasonably certain woman is not pregnant, first course can be started on any day of cycle); subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting and changing routines see under Indications and Dose above
- ² Dose 1 tablet daily for 28 days starting on day 1–5 of cycle with first active tablet (withdrawal bleeding occurs when inactive tablets being taken) (if reasonably certain woman is not pregnant, first course can be started on any day of cycle); subsequent courses repeated without interval; for starting and changing routines see under Indications and Dose above
- ³ Dose 1 tablet daily for 28 days starting on day 1 of cycle with first active tablet (withdrawal bleeding occurs when inactive tablets being taken); subsequent courses repeated without interval; for starting and changing routines see under Indications and Dose above

contraceptives offer a suitable alternative to combined hormonal contraceptives when oestrogens are contraindicated (including those with venous thrombosis or a past history or predisposition to venous thrombosis, heavy smokers, those with hypertension above systolic 160 mmHg or diastolic 95 mmHg, valvular heart disease, diabetes mellitus with complications, and migraine with aura). Menstrual irregularities (oligomenorrhoea, menorrhagia) are more common but tend to resolve on long-term treatment.

Interactions Effectiveness of oral progestogen-only preparations is not affected by antibacterials that do not induce liver enzymes. The efficacy of oral progestogen-only preparations is, however, reduced by enzyme-inducing drugs and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with an enzyme-inducing drug and for at least 4 weeks afterwards—see p. 402 and Appendix 1 (progestogens). For a short course of an enzyme-inducing drug, if a change in contraceptive method is undesirable or inappropriate, the progestogen-only oral method may be continued in combination with additional contraceptive precautions (e.g. barrier methods) for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping.

Surgery All progestogen-only contraceptives (including those given by injection) are suitable for use as an alternative to combined hormonal contraceptives before major elective surgery, before all surgery to the legs, or before surgery which involves prolonged immobilisation of a lower limb.

Starting routine One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 3 hours (12 hours for desogestrel) contraceptive protection may be lost). Additional contraceptive precautions are not necessary when initiating treatment.

Changing from a combined oral contraceptive Start on the day following completion of the combined oral contraceptive course without a break (or in the case of ED tablets omitting the inactive ones).

After childbirth Oral progestogen-only contraceptives can be started up to and including day 21 postpartum without the need for additional contraceptive precautions. If started more than 21 days postpartum, additional contraceptive precautions are required for 2 days.

Missed pill The following advice is recommended:

'If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than 3 hours (12 hours for desogestrel) overdue you are not protected. Continue normal pill-taking but you must also use another method, such as the condom, for the next 2 days.'

The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception (see p. 413) if one or more progestogen-only contraceptive tablets are missed or taken more than 3 hours (12 hours for desogestrel) late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.

Diarrhoea and vomiting Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking an oral progestogen-only contraceptive, another pill should be taken as soon as possible. If a replacement pill is not taken within 3

hours (12 hours for desogestrel) of the normal time for taking the progestogen-only pill, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery (see also under Missed pill above).

ORAL PROGESTOGEN-ONLY CONTRACEPTIVES

(Progestogen-only pill, 'POP')

Cautions arterial disease; sex-steroid dependent cancer; past ectopic pregnancy; malabsorption syndromes; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice; systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies; functional ovarian cysts; history of jaundice in pregnancy; **interactions:** see notes above and Appendix 1 (progestogens)

Other conditions The product literature advises caution in patients with history of thromboembolism, hypertension, diabetes mellitus and migraine; evidence for caution in these conditions is unsatisfactory

Contra-indications undiagnosed vaginal bleeding; severe arterial disease; acute porphyria (section 9.8.2); history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable

Hepatic impairment caution in active liver disease; and recurrent cholestatic jaundice, avoid in liver tumour

Pregnancy not known to be harmful

Breast-feeding progestogen-only contraceptives do not affect lactation; see also After Childbirth above

Side-effects menstrual irregularities (see also notes above); nausea, vomiting, headache, dizziness, breast discomfort, depression, skin disorders, disturbance of appetite, changes in libido

Breast cancer There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. A possible small increase in the risk of breast cancer should be weighed against the benefits

Licensed use consult product literature for the licensing status of individual preparations

Indications and dose

Contraception

• By mouth

1 tablet daily at same time each day, starting on day 1 of cycle then continuously; if administration delayed for 3 hours (12 hours for desogestrel) or more it should be regarded as a 'missed pill', see notes above

Desogestrel (Non-proprietary) (PoM)

Tablets, desogestrel 75 micrograms, net price 3 × 28-tab pack = £3.51

Brands include Aizea®, Cerelle®, Nacrez®

Cerazette® (MSD) (PoM)

Tablets, f/c, desogestrel 75 micrograms, net price 3 × 28-tab pack = £8.68

The Scottish Medicines Consortium (p. 3) has advised (September 2003) that Cerazette® should be restricted for use in women who cannot tolerate oestrogen-containing contraceptives or in whom such preparations are contraindicated

Micronor® (Janssen) (PoM)

Tablets, norethisterone 350 micrograms, net price 3 × 28-tab pack = £1.80

Norgeston® (Bayer) (PoM)

Tablets, s/c, levonorgestrel 30 micrograms, net price 35-tab pack = 92p

Noriday® (Pharmacia) (PoM)

Tablets, norethisterone 350 micrograms, net price 3 × 28-tab pack = £2.10

7.3.2.2 Parenteral progestogen-only contraceptives

Medroxyprogesterone acetate (*Depo-Provera®*, *SAYANA PRESS®*) is a long-acting progestogen given by injection; it is at least as effective as the combined oral preparations but because of its prolonged action it should never be given without *full counselling backed by the patient information leaflet*. It may be used as a short-term or long-term contraceptive for women who have been counselled about the likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility. Troublesome bleeding has been reported in patients given medroxyprogesterone acetate in the immediate puerperium; delaying the first injection until 6 weeks after the birth may minimise bleeding problems. If the woman is not breast-feeding, the first injection may be given within 5 days postpartum (she should be warned that the risk of troublesome bleeding may be increased). The manufacturers advise that in women who are breast-feeding, the first dose should be delayed until 6 weeks after the birth; however, evidence suggests no harmful effect to infant if given earlier. The benefits of using medroxyprogesterone acetate in breast-feeding women outweigh any risks.

Reduction in bone mineral density and, rarely, osteoporosis and osteoporotic fractures have also been reported with medroxyprogesterone acetate. The reduction in bone mineral density occurs in the first 2–3 years of use and then stabilises. See also below.

- In adolescents, medroxyprogesterone acetate (*Depo-Provera®*, *SAYANA PRESS®*) should be used only when other methods of contraception are inappropriate;
- in all women, the benefits of using medroxyprogesterone acetate beyond 2 years should be evaluated against the risks;
- in women with risk factors for osteoporosis, a method of contraception other than medroxyprogesterone acetate should be considered.

Norethisterone enantate (*Noristerat®*) is a long-acting progestogen given as an oily injection which provides contraception for 8 weeks; it is used as short-term interim contraception e.g. before vasectomy becomes effective.

An **etonogestrel-releasing implant** (*Nexplanon®*) is also available. It is a highly effective long-acting contraceptive, consisting of a single flexible rod that is inserted subdermally into the lower surface of the upper arm and provides contraception for up to 3 years. The manufacturer advises that in heavier women, blood-etonogestrel concentrations are lower and therefore the implant may not provide effective contraception during the third

year; they advise that earlier replacement may be considered in such patients, however, evidence to support this recommendation is lacking. Local reactions such as bruising and itching can occur at the insertion site. The contraceptive effect of etonogestrel is rapidly reversed on removal of the implant. *The doctor or nurse administering (or removing) the system should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.*

Implanon®, also an etonogestrel-releasing implant, has been discontinued (October 2010), but some women may have the implant in place until 2013.

Cautions, contra-indications, and side-effects

The cautions, contra-indications, and side-effects of oral progestogen-only contraceptives apply to parenteral progestogen-only contraceptives, except that parenteral preparations reliably inhibit ovulation and therefore protect against ectopic pregnancy and functional ovarian cysts.

Interactions Effectiveness of parenteral progestogen-only contraceptives is not affected by antibacterials that do not induce liver enzymes. The effectiveness of norethisterone intramuscular injection and medroxyprogesterone acetate intramuscular and subcutaneous injections is not affected by enzyme-inducing drugs and they may be continued as normal during courses of these drugs. However, effectiveness of the etonogestrel-releasing implant may be reduced by enzyme-inducing drugs and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with the enzyme-inducing drug and for at least 4 weeks after stopping. For a short course of an enzyme-inducing drug, if a change in contraceptive method is undesirable or inappropriate, the implant may be continued in combination with additional contraceptive precautions (e.g. condom) for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping it.

PARENTERAL PROGESTOGEN-ONLY CONTRACEPTIVES

Cautions see notes above and under preparations; possible risk of breast cancer, see oral progestogen-only contraceptives (section 7.3.2.1); history during pregnancy of pruritus or of deterioration of otosclerosis, disturbances of lipid metabolism; **interactions**: see notes above and Appendix 1 (progestogens)

Counselling Full counselling backed by *patient information leaflet* required before administration

Contra-indications see notes above; history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable

Hepatic impairment see Oral Progestogen-only Contraceptives, section 7.3.2.1

Pregnancy not known to be harmful; for *Implanon®* or *Nexplanon®* if pregnancy occurs remove implant

Breast-feeding progestogen-only contraceptives do not affect lactation; see also notes above

Side-effects see notes above; injection-site reactions; with medroxyprogesterone acetate injection, weight gain also reported

Cervical cancer Use of injectable progestogen-only contraceptives is associated with a small increased risk of cervical cancer; this increased risk may be similar to that seen with combined oral contraceptives, see p. 403. The risk

of cervical cancer with other progestogen-only contraceptives is not yet known.

Licensed use consult product literature for the licensing status of individual preparations

Indications and dose

Contraception see also notes above and under preparations (roles vary according to preparation)

For dose see under preparations

Injectable preparations

Depo-Provera® (Pfizer) (PoM)

Injection (aqueous suspension), medroxyprogesterone acetate 150 mg/mL, net price 1-mL prefilled syringe = £6.01, 1-mL vial = £6.01. Counselling, see patient information leaflet

Dose

• By deep intramuscular injection

150 mg within first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breast-feeding); for long-term contraception, repeated every 12 weeks (if interval greater than 12 weeks and 5 days, rule out pregnancy before next injection and advise patient to use additional contraceptive measures (e.g. barrier) for 14 days after the injection)

Noristerat® (Bayer) (PoM)

Injection (oily), norethisterone enantate 200 mg/mL, net price 1-mL amp = £4.05. Counselling, see patient information leaflet

Dose

• By deep intramuscular injection

Given very slowly *into gluteal muscle*, short-term contraception, 200 mg within first 5 days of cycle or immediately after parturition (duration 8 weeks); may be repeated once after 8 weeks (withhold breast-feeding for neonates with severe or persistent jaundice requiring medical treatment)

SAYANA PRESS® (Pfizer) (PoM)

Injection (suspension), medroxyprogesterone acetate 104 mg/0.65 mL, net price 0.65-mL prefilled injector device = £6.90. Counselling, see patient information leaflet

Dose

• By subcutaneous injection into anterior thigh or abdomen

No hormonal contraceptive use in previous month, 104 mg within first 5 days of cycle or within 5 days postpartum (delay until 6 weeks postpartum if breast-feeding); for long-term contraception, repeated every 13 weeks (if interval greater than 13 weeks and 7 days, rule out pregnancy before next injection); changing from other hormonal contraceptive, consult product literature

Implants

Nexplanon® (MSD) (PoM)

Implant, containing etonogestrel 68 mg in radiopaque flexible rod, net price = £79.46. Counselling, see patient information leaflet

Dose

• By subdermal implantation

No hormonal contraceptive use in previous month, 1 implant inserted during first 5 days of cycle; postpartum, 1 implant inserted 21–28 days after delivery; in breast-feeding mothers, 1 implant inserted after 28 days postpartum; abortion or miscarriage in the second trimester, 1 implant inserted 21–28 days after abortion or miscarriage; abortion or miscarriage in first trimester, 1 implant inserted within 5 days; changing from other hormonal contraceptive, consult product literature; remove implant within 3 years of insertion

7.3.2.3 Intra-uterine progestogen-only device

The progestogen-only intra-uterine system, *Mirena*®, releases **levonorgestrel** directly into the uterine cavity. It is used as a contraceptive, for the treatment of primary menorrhagia and for the prevention of endometrial hyperplasia during oestrogen replacement therapy. This may therefore be a contraceptive method of choice for women who have excessively heavy menses.

The effects of the progestogen-only intra-uterine system are mainly local and hormonal including prevention of endometrial proliferation, thickening of cervical mucus, and suppression of ovulation in some women (in some cycles). In addition to the progestogenic activity, the intra-uterine system itself may contribute slightly to the contraceptive effect. Return of fertility after removal is rapid and appears to be complete. *The doctor or nurse administering (or removing) the system should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.*

Advantages of the progestogen-only intra-uterine system over copper intra-uterine devices are that there may be an improvement in any dysmenorrhoea and a reduction in blood loss; there is also evidence that the frequency of pelvic inflammatory disease may be reduced (particularly in the youngest age groups who are most at risk).

In primary menorrhagia, menstrual bleeding is reduced significantly within 3–6 months of inserting the progestogen-only intra-uterine system, probably because it prevents endometrial proliferation. Another treatment should be considered if menorrhagia does not improve within this time (section 6.4.1.2).

Cautions and contra-indications Generally the cautions and contra-indications for the progestogen-only intra-uterine system are as for standard intra-uterine devices (section 7.3.4). Although the progestogen-only intra-uterine system produces little systemic progestogenic activity, it is usually avoided for 5 years after any evidence of breast cancer. However, the system can be considered for a woman in long-term remission from breast cancer who has menorrhagia and requires effective contraception. Since levonorgestrel is released close to the site of the main contraceptive action (on cervical mucus and endometrium) progestogenic side-effects and interactions are less likely; in particular, enzyme-inducing drugs are unlikely to significantly reduce the contraceptive effect of the progestogen-only intra-uterine system and additional contraceptive precautions are not required.

Side-effects Initially, changes in the pattern and duration of menstrual bleeding (spotting or prolonged bleeding) are common; endometrial disorders should be ruled out before insertion and the patient should be fully counselled (and provided with a patient information leaflet). Improvement in progestogenic side-effects, such as mastalgia and in the bleeding pattern usually occurs a few months after insertion and bleeding may often become very light or absent. Functional ovarian cysts (usually asymptomatic) can occur and usually resolve spontaneously (ultrasound monitoring recommended).

INTRA-UTERINE PROGESTOGEN-ONLY SYSTEM

Cautions see notes above; history of depression; advanced uterine atrophy; systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies; **interactions:** see notes above and Appendix 1 (progestogens)

Contra-indications see notes above; not suitable for emergency contraception

Hepatic impairment see Oral Progestogen-only Contraceptives, section 7.3.2.1

Pregnancy avoid; if pregnancy occurs remove system

Breast-feeding progestogen-only contraceptives do not affect lactation

Side-effects see notes above; also abdominal pain, expulsion, peripheral oedema, depression (sometimes severe), nervousness, salpingitis, pelvic inflammatory disease, pelvic pain, back pain; *rarely* uterine perforation, hirsutism, hair loss, pruritus, migraine, rash

Licensed use not licensed for use in women under 18 years

Indications and dose

See under preparation

Mirena® (Bayer) [PoM]

Intra-uterine system, T-shaped plastic frame (impregnated with barium sulfate and with threads attached to base) with polydimethylsiloxane reservoir releasing levonorgestrel 20 micrograms/24 hours, net price = £88.00. Counselling, see patient information leaflet

Dose

Contraception and menorrhagia

Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement, or any time if reasonably certain the woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately after first-trimester termination by curettage; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 5 years

Note When system is removed (and not immediately replaced) and pregnancy is not desired, remove during first few days of menstruation, otherwise additional precautions (e.g. barrier methods) should be used for at least 7 days before removal

Prevention of endometrial hyperplasia during oestrogen replacement therapy

Insert during last days of menstruation or withdrawal bleeding or anytime if amenorrhoeic; effective for 4 years

Products such as petroleum jelly (*Vaseline®*), baby oil and oil-based vaginal and rectal preparations are likely to damage condoms and contraceptive diaphragms made from latex rubber, and may render them less effective as a barrier method of contraception and as a protection from sexually transmitted infections (including HIV).

Gygel® (Marlborough)

Gel, nonoxinol '9' 2%, net price 30 g = £4.25

Excipients include hydroxybenzoates (parabens), propylene glycol, sorbic acid

Condoms No evidence of harm to latex condoms and diaphragms

Pregnancy toxicity in *animal* studies

Breast-feeding present in milk in *animal* studies

7.3.4 Contraceptive devices

Intra-uterine devices

The intra-uterine device (IUD) is a suitable contraceptive for women of all ages irrespective of parity; however, it is less appropriate for those with an increased risk of pelvic inflammatory disease e.g. women under 25 years (see below).

The most effective intra-uterine devices have at least 380 mm² of copper and have banded copper on the arms. Smaller devices have been introduced to minimise side-effects; these consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of the copper.

A frameless, copper-bearing intra-uterine device (*Gyne-Fix®*) is also available. It consists of a knotted, polypropylene thread with 6 copper sleeves; the device is anchored in the uterus by inserting the knot into the uterine fundus.

The timing and technique of fitting an intra-uterine device are critical for its subsequent performance. *The healthcare professional inserting (or removing) the device should be fully trained in the technique and should provide full counselling, backed, where available, by the patient information leaflet.* Devices should not be fitted during the heavy days of the period; they are best fitted after the end of menstruation and before the calculated time of implantation.

The main excess risk of infection occurs in the first 20 days after insertion and is believed to be related to existing carriage of a sexually transmitted infection. Women under 25 years are at a higher risk of sexually transmitted infections, and pre-insertion screening (for chlamydia, and depending on sexual history and local prevalence of disease, *Neisseria gonorrhoeae*) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appropriate prophylactic antibacterial cover should be given. The woman should be advised to attend *as an emergency* if she experiences sustained pain during the next 20 days.

An intra-uterine device should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential post-coital contraception should be considered.

Spermicidal contraceptives are useful additional safeguards but do **not** give adequate protection if used alone unless fertility is already significantly diminished. They have two components: a spermicide and a vehicle which itself may have some inhibiting effect on sperm activity. They are suitable for use with barrier methods, such as diaphragms or caps; however, spermicidal contraceptives are not generally recommended for use with condoms, as there is no evidence of any additional protection compared with non-spermicidal lubricants.

Spermicidal contraceptives are not suitable for use in those with or at high risk of sexually transmitted infections (including HIV); high frequency use of the spermicide nonoxinol '9' has been associated with genital lesions, which may increase the risk of acquiring these infections

If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible.

INTRA-UTERINE CONTRACEPTIVE DEVICES

Cautions see notes above; also anaemia, menorrhagia (progestogen intra-uterine system might be preferable, section 7.3.2.3), endometriosis, severe primary dysmenorrhoea, history of pelvic inflammatory disease, diabetes, fertility problems, nulliparity and young age, severely scarred uterus (including after endometrial resection) or severe cervical stenosis; drug- or disease-induced immunosuppression (risk of infection—avoid if marked immunosuppression); epilepsy (risk of seizure at time of insertion); increased risk of expulsion if inserted before uterine involution; gynaecological examination before insertion, 6–8 weeks after then annually but counsel women to seek medical attention promptly in case of significant symptoms, especially pain; anticoagulant therapy (avoid if possible)

Contra-indications severe anaemia, recent sexually transmitted infection (if not fully investigated and treated), unexplained uterine bleeding, distorted or small uterine cavity, genital malignancy, active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration), pelvic inflammatory disease, established or marked immunosuppression; *copper devices*: copper allergy, Wilson's disease, medical diathermy

Pregnancy remove device; if pregnancy occurs, increased likelihood that it may be ectopic

Breast-feeding not known to be harmful

Side-effects uterine or cervical perforation, displacement, expulsion; pelvic infection may be exacerbated, menorrhagia, dysmenorrhoea, allergy; *on insertion*: pain (alleviated by NSAID such as ibuprofen 30 minutes before insertion) and bleeding, occasionally epileptic seizure and vasovagal attack

Indications and dose

See notes above

Ancora® 375 Ag (RF Medical)

Intra-uterine device, copper wire with silver core, wound on vertical stem of U-shaped plastic carrier, surface area approx. 375 mm², impregnated with barium sulfate for radio-opacity, threads attached to base of vertical stem; preloaded in inserter, net price = £9.95

For uterine length over 6.5 cm; replacement every 5 years (see also notes above)

Ancora® 375 Cu (RF Medical)

Intra-uterine device, copper wire, wound on vertical stem of U-shaped plastic carrier, surface area approx. 375 mm², impregnated with barium sulfate for radio-opacity, threads attached to base of vertical stem; preloaded in inserter, net price = £7.95

For uterine length over 6.5 cm; replacement every 5 years (see also notes above)

Copper T 380A® (RF Medical)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper sleeve on each arm, total surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, threads attached to base of vertical stem; with loading capsule, net price = £8.95

For uterine length 6.5–9 cm; replacement every 10 years (see also notes above)

Cu-Safe® T300 (Williams)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 300 mm², impregnated with barium sulfate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £9.11

For uterine length over 5 cm; replacement every 5 years (see also notes above)

Flexi-T 300® (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 300 mm², impregnated with barium sulfate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £9.47

For uterine length over 5 cm; replacement every 5 years (see also notes above)

Flexi-T® + 380 (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper sleeve on each arm, total surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £10.06

For uterine length over 6 cm; replacement every 5 years (see also notes above)

GyneFix® (Williams)

Intra-uterine device, 6 copper sleeves with surface area of 330 mm² on polypropylene thread, net price = £27.11

Suitable for all uterine sizes; replacement every 5 years

Load® 375 (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of U-shaped plastic carrier, surface area approx. 375 mm², impregnated with barium sulfate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £8.52

For uterine length over 7 cm; replacement every 5 years (see also notes above)

Mini TT 380® Slimline (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper sleeves fitted flush on to distal portion of each horizontal arm, total surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, thread attached to base of vertical stem; easy-loading system, no capsule, net price = £12.46

For minimum uterine length 5 cm; replacement every 5 years (see also notes above)

Multiload® Cu375 (MSD)

Intra-uterine device, as *Load® 375*, with copper surface area approx. 375 mm² and vertical stem length 3.5 cm, net price = £9.24

For uterine length 6–9 cm; replacement every 5 years (see also notes above)

Multi-Safe® 375 (Williams)

Intra-uterine device, copper wire, wound on vertical stem of U-shaped plastic carrier, surface area approx. 375 mm², impregnated with barium sulfate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £8.96

For uterine length 6–9 cm; replacement every 5 years (see also notes above)

MultiSafe® 375 Short Stem (Williams) 

Intra-uterine device, copper wire, wound on vertical stem of U-shaped plastic carrier, surface area approx. 375 mm², impregnated with barium sulfate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £8.80

For uterine length 5–7 cm; replacement every 5 years (see also notes above)

Neo-Safe® T380 (Williams)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, threads attached to base of vertical stem, net price = £13.31

For uterine length 6.5–9 cm; replacement every 5 years (see also notes above)

Novaplus T 380® Ag (RF Medical)

Intra-uterine device, copper wire with silver core, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, threads attached to base of vertical stem, net price = £12.50

'Mini' size for minimum uterine length 5 cm; 'Normal' size for uterine length 6.5–9 cm; replacement every 5 years (see also notes above)

Novaplus T 380® Cu (RF Medical)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, threads attached to base of vertical stem, net price = £10.95


'Mini' size for minimum uterine length 5 cm; 'Normal' size for uterine length 6.5–9 cm; replacement every 5 years (see also notes above)

Nova-T® 380 (Bayer)

Intra-uterine device, copper wire with silver core, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, threads attached to base of vertical stem, net price = £15.20

For uterine length 6.5–9 cm; replacement every 5 years (see also notes above)

T-Safe® 380A Quickload (Williams)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper collar on the distal portion of each arm, total surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, threads attached to base of vertical stem, net price = £10.29; available with a capsule loading device (*T-Safe® CU 380A* ) , net price £10.29

For uterine length 6.5–9 cm; replacement every 10 years (see also notes above)

TT 380® Stimline (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, with copper sleeves fitted flush on to distal portion of each horizontal arm, total surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, thread attached to base of vertical stem; easy-loading system, no capsule, net price = £12.46

For uterine length 6.5–9 cm; replacement every 10 years (see also notes above)

UT 380 Short® (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, thread attached to base of vertical stem; net price = £11.22

For uterine length 5–7 cm; replacement every 5 years (see also notes above)

UT 380 Standard® (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm², impregnated with barium sulfate for radio-opacity, thread attached to base of vertical stem; net price = £11.22

For uterine length 6.5–9 cm; replacement every 5 years (see also notes above)

Other contraceptive devices**▲ Silicone contraceptive caps****Silicone Contraceptive Pessary**

Silicone, sizes 22, 26, and 30 mm, net price = £15.00

Brands include FemCap®

▲ Rubber contraceptive diaphragms**Type A Diaphragm with Flat Metal Spring**

Transparent rubber with flat metal spring, sizes 55–95 mm (rising in steps of 5 mm), net price = £5.78

Brands include Reflexions®

▲ Silicone contraceptive diaphragms**Type B Diaphragm with Coiled Metal Spring**

Silicone with coiled metal spring, sizes 60–90 mm (rising in steps of 5 mm), net price = £8.35

Brands include Millex Omniflex®

Type C Arcing Spring diaphragm

Silicone with arcing spring, sizes 60–90 mm (rising in steps of 5 mm), net price = £8.35

Brands include Millex Arcing Style®, Ortho All-Flex®

7.3.5 Emergency contraception**Hormonal methods**

Hormonal emergency contraceptives include **levonorgestrel** and **ulipristal**; either drug should be taken as soon as possible after unprotected intercourse to increase efficacy.

Levonorgestrel is effective if taken within 72 hours (3 days) of unprotected intercourse and may also be used between 72 and 96 hours after unprotected intercourse [unlicensed use], but efficacy decreases with time. Ulipristal, a progesterone receptor modulator, is effective if taken within 120 hours (5 days) of unprotected intercourse.

Levonorgestrel is less effective than insertion of an intra-uterine device (see below). Ulipristal is as effective as levonorgestrel but its efficacy compared to an intra-uterine device is not yet known.

If vomiting occurs within 2 hours of taking levonorgestrel or within 3 hours of taking ulipristal, a replacement dose should be given.

When prescribing or supplying hormonal emergency contraception, women should be advised:

- that their next period may be early or late;

- that a barrier method of contraception needs to be used until the next period;
- to seek medical attention promptly if any lower abdominal pain occurs because this could signify an ectopic pregnancy;
- to return in 3 to 4 weeks if the subsequent menstrual bleed is abnormally light, heavy or brief, or is absent, or if she is otherwise concerned (if there is any doubt as to whether menstruation has occurred, a pregnancy test should be performed at least 3 weeks after unprotected intercourse).

Interactions The effectiveness of levonorgestrel, and possibly ulipristal is reduced in women taking enzyme-inducing drugs (and possibly for 4 weeks after stopping); a copper intra-uterine device can be offered instead. If the copper intra-uterine device is undesirable or inappropriate, the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose [unlicensed dose—advise women accordingly]. There is no need to increase the dose for emergency contraception if the patient is taking antibacterials that are not enzyme inducers.

LEVONORGESTREL

Cautions see notes above; past ectopic pregnancy; severe malabsorption syndromes; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice; **interactions:** see notes above and Appendix 1 (progestogens)

Contra-indications acute porphyria (section 9.8.2)

Pregnancy not known to be harmful

Breast-feeding progestogen-only contraceptives do not affect lactation

Side-effects menstrual irregularities (see also notes above), nausea, low abdominal pain, fatigue, headache, dizziness, breast tenderness, vomiting

Licensed use consult product literature

Indications and dose

Emergency contraception

- By mouth

1.5 mg as a single dose as soon as possible after coitus, preferably within 12 hours but no later than after 72 hours (but see also notes above)

¹Levonelle® One Step (Bayer)

Tablets, levonorgestrel 1.5 mg, net price 1-tab pack = £13.83

Levonelle® 1500 (Bayer) (PoM)

Tablets, levonorgestrel 1.5 mg, net price 1-tab pack = £5.20

ULIPRISTAL ACETATE

Cautions see notes above; uncontrolled severe asthma; effectiveness of combined hormonal and progestogen-only contraceptives may be reduced—additional precautions (barrier methods) required for 14 days for combined and parenteral progestogen-only hormonal contraceptives (16 days for *Qlaira*®) and 9 days for oral progestogen-only contraceptives;

1. Can be sold to women over 16 years; when supplying emergency contraception to the public, pharmacists should refer to guidance issued by the Royal Pharmaceutical Society

interactions: see notes above and Appendix 1 (ulipristal)

Contra-indications repeated use within a menstrual cycle

Hepatic impairment manufacturer advises avoid in severe impairment—no information available

Pregnancy limited information available

Breast-feeding manufacturer advises avoid for 1 week after administration—present in milk

Side-effects gastro-intestinal disturbances (including nausea, vomiting, diarrhoea, and abdominal pain); dizziness, fatigue, headache, menstrual irregularities (see notes above); back pain, muscle spasms; *less commonly* tremor, hot flushes, uterine spasm, breast tenderness, dry mouth, blurred vision, pruritus, and rash

Indications and dose

Emergency contraception

- By mouth

30 mg as a single dose as soon as possible after coitus, but no later than after 120 hours

ellaOne® (HRA Pharma) (PoM)

Tablets, ulipristal acetate 30 mg, net price 1-tab pack = £16.95

Intra-uterine device

Insertion of an intra-uterine device is more effective than oral levonorgestrel for emergency contraception, see also notes above. A copper intra-uterine contraceptive device (section 7.3.4) can be inserted up to 120 hours (5 days) after unprotected intercourse; sexually transmitted infections should be tested for and insertion of the device should usually be covered by antibacterial prophylaxis (e.g. azithromycin 1 g by mouth as a single dose). If intercourse has occurred more than 5 days previously, the device can still be inserted up to 5 days after the earliest likely calculated ovulation (i.e. within the minimum period before implantation), regardless of the number of episodes of unprotected intercourse earlier in the cycle.

7.4 Drugs for genito-urinary disorders

7.4.1 Drugs for urinary retention

7.4.2 Drugs for urinary frequency, enuresis, and incontinence

7.4.3 Drugs used in urological pain

7.4.4 Bladder instillations and urological surgery

7.4.5 Drugs for erectile dysfunction

For drugs used in the treatment of urinary-tract infections see section 5.1.13.

7.4.1 Drugs for urinary retention

Acute retention is painful and is treated by catheterisation.

Chronic retention is painless and often long-standing. Clean intermittent catheterisation may be considered. After the cause has been established and treated, drugs may be required to increase detrusor muscle tone.

Alpha-blockers such as doxazosin and tamsulosin can be used in some cases of dysfunctional voiding.

Alpha-blockers

The selective alpha-blockers **doxazosin** and **tamsulosin** can be used to improve bladder emptying in children with dysfunctional voiding where the post-void residual urine volume is significant; treatment should be under specialist advice only. Alpha-blockers can reduce blood pressure rapidly after the first dose and should be introduced with caution.

DOXAZOSIN

Cautions see under Doxazosin (section 2.5.4)

Contra-indications see under Doxazosin (section 2.5.4)

Hepatic impairment see under Doxazosin (section 2.5.4)

Pregnancy see under Doxazosin (section 2.5.4)

Breast-feeding see under Doxazosin (section 2.5.4)

Side-effects see under Doxazosin (section 2.5.4)

Licensed use not licensed for use in children

Indications and dose

Dysfunctional voiding (see notes above)

- By mouth

Child 4–12 years initially 0.5 mg daily increased at monthly intervals according to response; maximum 2 mg daily

Child 12–18 years initially 1 mg daily, dose may be doubled at intervals of 1 month according to response; usual maintenance 2–4 mg daily; max. 8 mg daily

Hypertension section 2.5.4

Preparations

Section 2.5.4

TAMSULOSIN HYDROCHLORIDE

Cautions care with initial dose (postural hypotension); cataract surgery (risk of intra-operative floppy iris syndrome); **interactions:** Appendix 1 (alpha-blockers)

Driving May affect performance of skilled tasks e.g. driving

Contra-indications history of postural hypotension

Hepatic impairment avoid in severe impairment

Renal impairment use with caution if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Side-effects dizziness, headache, asthenia; abnormal ejaculation; *less commonly* nausea, vomiting, constipation, diarrhoea, palpitation, postural hypotension, syncope, rhinitis, rash, pruritus, and urticaria; *very rarely* angioedema and priapism; also drowsiness, blurred vision, dry mouth, and oedema; *also reported* intra-operative floppy iris syndrome

Licensed use not licensed for use in children

Indications and dose

Dysfunctional voiding (see notes above)

- By mouth

Child 12–18 years 400 micrograms once daily

Tamsulosin hydrochloride (Non-proprietary) (PoM)

Capsules, m/r, tamsulosin hydrochloride 400 micrograms, net price 30-cap pack = £5.10. Label: 25, counselling, driving

Brands include *Bazetham*® MR, *Contiflo*® XL, *Diffundox*® XL, *Losinate*® MR, *Pinexel*® PR, *Prosurin*® XL, *Stronazon*® MR, *Tabphyn*® MR

Flomaxtra® XL (Astellas) (PoM)

Tablets, m/r, tamsulosin hydrochloride 400 micrograms, net price 30-tab pack = £10.47. Label: 25, counselling, driving

7.4.2 Drugs for urinary frequency, enuresis, and incontinence

Urinary incontinence

Antimuscarinic drugs reduce symptoms of urgency and urge incontinence and increase bladder capacity; **oxybutynin** also has a direct relaxant effect on urinary smooth muscle. Oxybutynin can be considered first for children under 12 years. Side-effects limit the use of oxybutynin, but they may be reduced by starting at a lower dose and then slowly titrating upwards; alternatively oxybutynin can be given by intravesicular instillation. **Tolterodine** is also effective for urinary incontinence; it can be considered for children over 12 years, or for younger children who have failed to respond to oxybutynin. Modified-release preparations of oxybutynin and tolterodine are available; they may have fewer side-effects. Antimuscarinic treatment should be reviewed soon after it is commenced, and then at regular intervals; a response generally occurs within 6 months but occasionally may take longer. Children with nocturnal enuresis may require specific additional measures if night-time symptoms also need to be controlled (see p. 416).

Cautions Antimuscarinic drugs should be used with caution in autonomic neuropathy and in children susceptible to angle-closure glaucoma. Antimuscarinics can worsen hyperthyroidism, congestive heart failure, arrhythmias, and tachycardia. For **interactions**, see Appendix 1 (antimuscarinics).

Contra-indications Antimuscarinic drugs should be avoided in myasthenia gravis, significant bladder outflow obstruction or urinary retention, severe ulcerative colitis, toxic megacolon, and in gastro-intestinal obstruction or intestinal atony.

Side-effects Side-effects of antimuscarinic drugs include dry mouth, gastro-intestinal disturbances including constipation, blurred vision, dry eyes, drowsiness, difficulty in micturition (less commonly urinary retention), palpitation, and skin reactions (including dry skin, rash, and photosensitivity); also headache, diarrhoea, angioedema, arrhythmias, and tachycardia. Central nervous system stimulation, such as restlessness, disorientation, hallucination, and convulsions may occur. Antimuscarinic drugs may reduce sweating leading to heat sensations and fainting in hot environments or in patients with fever, and *very rarely* may precipitate angle-closure glaucoma.

OXYBUTYNIN HYDROCHLORIDE

Cautions see notes above; acute porphyria (section 9.8.2)

Contra-indications see notes above

Hepatic impairment manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy manufacturer advises avoid unless essential—toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects see notes above; also dizziness; *less commonly* anorexia, facial flushing; *rarely* night terrors

Licensed use not licensed for use in children under 5 years; intravesical instillation not licensed for use in children

Indications and dose

Urinary frequency, urgency and incontinence, neurogenic bladder instability

• By mouth

Child 2–5 years 1.25–2.5 mg 2–3 times daily;

Child 5–12 years 2.5–3 mg twice daily, increased to 5 mg 2–3 times daily

Child 12–18 years 5 mg 2–3 times daily, increased if necessary to max. 5 mg 4 times daily

• By intravesical instillation

Child 2–18 years 5 mg 2–3 times daily

Nocturnal enuresis associated with overactive bladder

• By mouth

Child 5–18 years 2.5–3 mg twice daily increased to 5 mg 2–3 times daily (last dose before bedtime)

Oxybutynin Hydrochloride (Non-proprietary) (PoM)

Tablets, oxybutynin hydrochloride 2.5 mg, net price 56-tab pack = £1.81; 3 mg, 56-tab pack = £14.00; 5 mg, 56-tab pack = £2.71, 84-tab pack = £4.45. Label: 3

Intravesical instillation, oxybutynin (as hydrochloride) 5 mg/30 mL.

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Cystrin® (Winthrop) (PoM)

Tablets, oxybutynin hydrochloride 5 mg (scored), net price 84-tab pack = £21.99. Label: 3

Ditropan® (Sanofi-Aventis) (PoM)

Tablets, both blue, scored, oxybutynin hydrochloride 2.5 mg, net price 84-tab pack = £1.60; 5 mg, 84-tab pack = £2.90. Label: 3

Ellixir, oxybutynin hydrochloride 2.5 mg/5 mL, net price 150-mL pack = £6.88. Label: 3

Modified release

Lyrinel® XL (Janssen) (PoM)

Tablets, m/r, oxybutynin hydrochloride 5 mg (yellow), net price 30-tab pack = £13.77; 10 mg (pink), 30-tab pack = £27.54. Label: 3, 25

Dose

Urinary frequency, urgency, and incontinence associated with idiopathic overactive bladder or neurogenic bladder instability; nocturnal enuresis associated with overactive bladder (see also Nocturnal Enuresis, p. 416)

• By mouth

Child 5–18 years initially 5 mg once daily adjusted according to response in steps of 5 mg at weekly intervals; max. 15 mg once daily

Note Children taking immediate-release oxybutynin may be transferred to the nearest equivalent daily dose of *Lyrinel® XL*

TOLTERODINE TARTRATE

Cautions see notes above; history of QT-interval prolongation; concomitant use with other drugs known to prolong QT interval

Contra-indications see notes above

Hepatic impairment reduce dose; avoid modified-release preparations

Renal impairment reduce dose and avoid modified-release preparations if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above; also chest pain, peripheral oedema; sinusitis, bronchitis; paraesthesia, fatigue, dizziness, vertigo, weight gain; *less commonly* memory impairment; *also reported* flushing

Licensed use not licensed for use in children

Indications and dose

Urinary frequency, urgency, incontinence

• By mouth

Child 2–18 years 1 mg once daily, increased according to response; max. 2 mg twice daily

Nocturnal enuresis associated with overactive bladder

• By mouth

Child 5–18 years 1 mg once daily at bedtime, increased according to response; max. 2 mg twice daily

Tolterodine Tartrate (Non-proprietary) (PoM)

Tablets, tolterodine tartrate 1 mg, net price 56-tab pack = £2.72; 2 mg, 56-tab pack = £2.68. Label: 3

Detrusitol® (Pfizer) (PoM)

Tablets, f/c, tolterodine tartrate 1 mg, net price 56-tab pack = £29.03; 2 mg, 56-tab pack = £30.56

Modified release

Tolterodine Tartrate (Non-proprietary) (PoM)

Capsules, m/r, tolterodine tartrate 4 mg, net price 28-cap pack = £25.78. Label: 3, 25

Brands include *Santizor XL®*

Note Children stabilised on immediate-release tolterodine tartrate 2 mg twice daily may be transferred to modified-release tolterodine tartrate 4 mg once daily

Detrusitol® XL (Pfizer) (PoM)

Capsules, blue, m/r, tolterodine tartrate 4 mg, net price 28-cap pack = £25.78. Label: 25

Note Children stabilised on immediate-release tolterodine tartrate 2 mg twice daily may be transferred to *Detrusitol® XL* 4 mg once daily

Nocturnal enuresis in children

Nocturnal enuresis is common in young children, but persists in a small proportion by 10 years of age. For children under 5 years, reassurance and advice on the management of nocturnal enuresis can be useful for some families. Treatment may be considered in children over 5 years depending on their maturity and motivation, the frequency of nocturnal enuresis, and the needs of the child and their family.

Initially, advice should be given on fluid intake, diet, toileting behaviour, and reward systems; for children who do not respond to this advice, further treatment

may be necessary. An **enuresis alarm** should be first-line treatment for motivated, well supported children; alarms have a lower relapse rate than drug treatment when discontinued. Treatment should be reviewed after 4 weeks, and, if there are early signs of response, continued until a minimum of 2 weeks' uninterrupted dry nights have been achieved. If complete dryness is not achieved after 3 months, only continue if the condition is still improving and the child remains motivated to use the alarm. If initial alarm treatment is unsuccessful, consider combination treatment with **desmopressin** (see below), or desmopressin alone if the alarm is no longer appropriate or desirable.

Desmopressin (section 6.5.2), an analogue of vasopressin, is given by oral or by sublingual administration; it should not be given intranasally for nocturnal enuresis due to an increased incidence of side-effects. Desmopressin alone can be offered to children over 5 years of age if an alarm is inappropriate or undesirable, or when rapid or short-term results are the priority (for example to cover periods away from home); desmopressin alone can also be used if there has been a partial response to a combination of desmopressin and an alarm following initial treatment with an alarm. Treatment should be assessed after 4 weeks and continued for 3 months if there are signs of response. Desmopressin should be withdrawn at regular intervals (for 1 week every 3 months) for full reassessment. Particular care is needed to avoid fluid overload by restricting fluid intake from 1 hour before taking desmopressin until 8 hours after. When stopping treatment with desmopressin, gradual withdrawal should be considered.

Nocturnal enuresis associated with daytime symptoms (overactive bladder) can be managed with antimuscarinic drugs (see Urinary incontinence, p. 415) in combination with desmopressin. Treatment should be prescribed only after specialist assessment and should be continued for 3 months; the course can be repeated if necessary.

The tricyclic antidepressant **imipramine** (section 4.3.1) may be considered for children who have not responded to all other treatments and have undergone specialist assessment, however, behavioural disturbances can occur and relapse is common after withdrawal. Treatment should not normally exceed 3 months unless a physical examination is made and the child is fully reassessed; toxicity following overdosage with tricyclics is of particular concern.

7.4.3 Drugs used in urological pain

Lidocaine gel is a useful topical application in *urethral pain* or to relieve the discomfort of catheterisation (section 15.2).

Alkalinisation of urine

Alkalinisation of urine can be undertaken with **potassium citrate**. The alkalinising action may relieve the discomfort of *cystitis* caused by lower urinary tract infections.

POTASSIUM CITRATE

Cautions cardiac disease; **interactions:** Appendix 1 (potassium salts)

Renal impairment close monitoring required—high risk of hyperkalaemia; avoid in severe impairment

Side-effects hyperkalaemia on prolonged high dosage, mild diuresis

Indications and dose

Relief of discomfort in mild urinary-tract infections, alkalinisation of urine for dose see preparations below

Potassium Citrate Mixture BP

(Potassium Citrate Oral Solution)

Oral solution, potassium citrate 30%, citric acid monohydrate 5% in a suitable vehicle with a lemon flavour. Extemporaneous preparations should be recently prepared according to the following formula: potassium citrate 3 g, citric acid monohydrate 500 mg, syrup 2.5 mL, quillaia tincture 0.1 mL, lemon spirit 0.05 mL, double-strength chloroform water 3 mL, water to 10 mL. Contains about 28 mmol K⁺/10 mL. Label: 27

Dose

• By mouth

Child 1–6 years 5 mL 3 times daily well diluted with water

Child 6–18 years 10 mL 3 times daily well diluted with water

Note Proprietary brands of potassium citrate are on sale to the public for the relief of discomfort in mild urinary-tract infections

7.4.4 Bladder instillations and urological surgery

Bladder infection Various solutions are available as irrigations or washouts.

Aqueous **chlorhexidine** (section 13.11.2) can be used in the management of common infections of the bladder but it is ineffective against most *Pseudomonas* spp. Solutions containing chlorhexidine 1 in 5000 (0.02%) are used, but they may irritate the mucosa and cause burning and haematuria (in which case they should be discontinued); sterile **sodium chloride solution** 0.9% (physiological saline) is usually adequate and is preferred as a mechanical irrigant.

Dissolution of blood clots Clot retention is usually treated by irrigation with sterile **sodium chloride solution** 0.9% but sterile **sodium citrate solution** for bladder irrigation 3% may also be helpful.

Maintenance of indwelling urinary catheters

The deposition which occurs in catheterised patients is usually chiefly composed of phosphate and to minimise this the catheter (if latex) should be changed at least as often as every 6 weeks. If the catheter is to be left for longer periods a silicone catheter should be used together with the appropriate use of catheter maintenance solutions. Repeated blockage usually indicates that the catheter needs to be changed.

CATHETER PATENCY SOLUTIONS

Chlorhexidine 0.02%

Brands include *Uro-Tainer Chlorhexidine*®, net price 100-mL sachet = £2.70

Sodium chloride 0.9%

Brands include *OptiFlo S*®, net price 50- and 100-mL sachets = £3.30; *Urilflex S*®, 100-mL sachet = £3.45; *Urilflex SP*®, with integral drug additive port, 100-mL sachet = £3.45; *Uro-Tainer Sodium Chloride*®, 50- and 100-mL sachets = £3.45; *Uro-Tainer M*®, with integral drug additive port, 50- and 100-mL sachets = £2.90

Solution G

Citric acid 3.23%, magnesium oxide 0.38%, sodium bicarbonate 0.7%, disodium edetate 0.01%. Brands include *OptiFlo G*®, net price 50- and 100-mL sachets = £3.50; *Urilflex G*®, 100-mL sachet = £2.40; *Uro-Tainer*® *Twin Suby G*, 2 × 30-mL = £4.72

Solution R

Citric acid 6%, gluconolactone 0.6%, magnesium carbonate 2.8%, disodium edetate 0.01%. Brands include *OptiFlo R*®, net price 50- and 100-mL sachets = £3.50; *Urilflex R*®, 100-mL sachet = £2.40; *Uro-Tainer*® *Twin Solutio R*, 2 × 30-mL = £4.72

Diluents for bladder instillation**SODIUM CHLORIDE****Indications and dose**

Diluent for instillation of drugs to the bladder
consult product literature

Sodium Chloride 0.9% Solution for Intravesical**Use** (Non-proprietary)

Intravesical instillation, sodium chloride 0.9%, net price 50-mL bag = £9.66

7.4.5 Drugs for erectile dysfunction

This section is not included in *BNF for Children*. Adolescents presenting with erectile dysfunction should be referred to a specialist.

7.4.6 Drugs for premature ejaculation

This section is not included in *BNF for Children*.

8 Malignant disease and immunosuppression

8.1 Cytotoxic drugs	419
8.1.1 Alkylating drugs	424
8.1.2 Cytotoxic antibiotics	426
8.1.3 Antimetabolites	428
8.1.4 Vinca alkaloids and etoposide	430
8.1.5 Other antineoplastic drugs	432
8.2 Drugs affecting the immune response	435
8.2.1 Antiproliferative immunosuppressants	436
8.2.2 Corticosteroids and other immunosuppressants	437
8.2.3 Anti-lymphocyte monoclonal antibodies	444
8.2.4 Other immunomodulating drugs	444
8.3 Sex hormones and hormone antagonists in malignant disease	447

8.1 Cytotoxic drugs

8.1.1 Alkylating drugs
8.1.2 Cytotoxic antibiotics
8.1.3 Antimetabolites
8.1.4 Vinca alkaloids and etoposide
8.1.5 Other antineoplastic drugs

The management of childhood cancer is complex and is generally confined to specialist regional centres and some associated shared-care units.

Cytotoxic drugs have both anti-cancer activity and the potential for damage to normal tissue. In children, chemotherapy is almost always started with curative intent, but may be continued as palliation if the disease is refractory.

Chemotherapy with a combination of two or more cytotoxic drugs aims to reduce the development of resistance and to improve cytotoxic effect. Treatment protocols generally incorporate a series of treatment courses at defined intervals with clear criteria for starting each course, such as adequate bone-marrow recovery and renal or cardiac function. The principal component of treatment for leukaemias in children is cytotoxic therapy, whereas solid tumours may be managed with surgery or radiotherapy in addition to chemotherapy.

Guidelines for handling cytotoxic drugs

- Trained personnel should reconstitute cytotoxics;
- Reconstitution should be carried out in designated pharmacy areas;
- Protective clothing (including gloves, gowns, and masks) should be worn;
- The eyes should be protected and means of first aid should be specified;
- Pregnant staff should avoid exposure to cytotoxic drugs (all females of child-bearing age should be informed of the reproductive hazard);
- Use local procedures for dealing with spillages and safe disposal of waste material, including syringes, containers, and absorbent material;
- Staff exposure to cytotoxic drugs should be monitored.

Only medical or nursing staff who have received appropriate training should administer parenteral cytotoxics. In most instances central venous access will be required for the intravenous administration of cytotoxics to children; care is required to avoid the risk of extravasation (see Side-effects of Cytotoxic Drugs and their Management).

Intrathecal chemotherapy

A Health Service Circular (HSC 2008/001) provides guidance on the introduction of safe practice in NHS Trusts where intrathecal chemotherapy is administered; written local guidance covering all aspects of national guidance should be available. Support for training programmes is also available.

Copies, and further information may be obtained from:

Department of Health
PO Box 777
London SE1 6XH
Fax: 01623 724524
www.dh.gov.uk

Safe system requirements for cytotoxic medicines:

- Cytotoxic drugs for the treatment of cancer should be given as part of a wider pathway of care that is co-ordinated by a multi-disciplinary team;
- Cytotoxic drugs should be prescribed, dispensed and administered only in the context of a written protocol or treatment plan;
- Injectable cytotoxic drugs should only be dispensed if they are prepared for administration;
- Oral cytotoxic medicines should be dispensed with clear directions for use.

Risks of incorrect dosing of oral anti-cancer medicines

The National Patient Safety Agency has advised (January 2008) that the prescribing and use of oral cytotoxic medicines should be carried out to the same standard as parenteral cytotoxic therapy. Standards to be followed to achieve this include:

- non-specialists who prescribe or administer oral cytotoxic medication should have access to written protocols and treatment plans, including guidance on the monitoring and treatment of toxicity
- staff dispensing oral cytotoxic medicines should confirm that the prescribed dose is appropriate for the patient. Patients and their carers should have written information that includes details of the intended oral anti-cancer regimen, the treatment plan, and arrangements for monitoring, taken from the original protocol from the initiating hospital. Staff dispensing oral cytotoxic medicines should also have access to this information, and to advice from an experienced cancer pharmacist in the initiating hospital

Doses

Doses of cytotoxic drugs are determined using a variety of different methods including age, body-surface area, or body-weight. Alternatively, doses may be fixed. Doses may be further adjusted following consideration of a patient's neutrophil count, renal and hepatic function, and history of previous adverse effects to the cytotoxic drug. Doses may also differ depending on whether a drug is used alone or in combination.

Because of the complexity of dosage regimens in the treatment of malignant disease, dose statements have been omitted from many of the drug entries in this chapter.

Side-effects of cytotoxic drugs and their management

Side-effects common to most cytotoxic drugs are discussed below whilst side-effects characteristic of a particular drug or class of drugs (e.g. neurotoxicity with vinca alkaloids) are mentioned in the appropriate sections. Manufacturers' product literature, hospital-trust protocols, and treatment protocols should be consulted for full details of side-effects of individual drugs.

Side-effects of cytotoxic drugs often do not occur at the time of administration, but days or weeks later. It is therefore important that children, their carers, and healthcare professionals can identify symptoms that cause concern and can contact an expert for advice. Toxicities should be accurately recorded using a recognised scoring system such as the Common Toxicity Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute.

Extravasation of intravenous drugs A number of cytotoxic drugs will cause severe local tissue irritation and necrosis if leakage into the extravascular compartment occurs. For information on the prevention and management of extravasation injury, see section 10.3.

Gastro-intestinal effects Management of gastro-intestinal effects of cytotoxic drugs includes the use of antacids, H_2 -receptor antagonists, and proton pump inhibitors to protect the gastric mucosa, laxatives to treat constipation, and enteral and parenteral nutritional support.

Oral mucositis Good oral hygiene keeps the mouth clean and moist and helps to prevent mucositis; prevention is more effective than treatment of the complication. Good oral hygiene measures for children over 6 months include brushing teeth with a soft small brush with fluoride toothpaste 2–3 times daily, and rinsing the mouth frequently. Daily fluoride supplements (section 9.5.3) can be used on the advice of the child's dental team. For children under 6 months or when it is not possible to brush teeth, carers should be instructed how to clean the mouth using an oral sponge moistened with water or with an antimicrobial solution such as diluted chlorhexidine. Mucositis related to chemotherapy can be extremely painful and may, in some circumstances, require opioid analgesia (section 4.7.2). Secondary infection with candida is frequent; treatment with a systemically absorbed antifungal, such as fluconazole (section 5.2), is effective.

Nausea and vomiting Nausea and vomiting cause considerable distress to many children who receive chemotherapy, and to a lesser extent abdominal radiotherapy, and may lead to refusal of further treatment; prophylaxis of nausea and vomiting is therefore extremely important. Symptoms may be acute (occurring within 24 hours of treatment), delayed (first occurring more than 24 hours after treatment), or anticipatory (occurring prior to subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management.

Susceptibility to nausea and vomiting may increase with repeated exposure to the cytotoxic drug.

Drugs may be divided according to their emetogenic potential and some examples are given below, but the symptoms vary according to the dose, to other drugs administered, and to the individual's susceptibility to emetogenic stimuli.

Mildly emetogenic treatment—fluorouracil, etoposide, low doses of methotrexate, the vinca alkaloids, and abdominal radiotherapy.

Moderately emetogenic treatment—carboplatin, doxorubicin, intermediate and low doses of cyclophosphamide, mitoxantrone, and high doses of methotrexate.

Highly emetogenic treatment—cisplatin, dacarbazine, and high doses of alkylating drugs.

Anti-emetic drugs, when given regularly, help prevent or ameliorate emesis associated with chemotherapy in children.

Prevention of acute symptoms For patients at *low risk of emesis*, pretreatment with a 5HT₃-receptor antagonist (section 4.6) may be of benefit.

For patients at *high risk of emesis* or when other treatment is inadequate, a 5HT₃-receptor antagonist (section 4.6) is often highly effective. The addition of dexamethasone and other anti-emetics may also be required.

Prevention of delayed symptoms Dexamethasone, given by mouth, is the drug of choice for preventing delayed symptoms; it is used alone or with metoclopramide. Due to the risks of neurological side-effects, metoclopramide should only be used in children as a second-line option (see section 4.6). The 5HT₃-receptor antagonists may have a role in preventing uncontrolled symptoms.

Prevention of anticipatory symptoms Good symptom control is the best way to prevent anticipatory symptoms. Lorazepam can be helpful for its amnesiac, sedative, and anxiolytic effects.

Bone-marrow suppression All cytotoxic drugs except vincristine and bleomycin cause bone-marrow suppression. This commonly occurs 7 to 10 days after administration, but is delayed for certain drugs, such as melphalan. Peripheral blood counts must be checked before each treatment. The duration and severity of neutropenia can be reduced by the use of granulocyte-colony stimulating factors (section 9.1.6); their use should be reserved for children who have previously experienced severe neutropenia.

Cytotoxic drugs may be contra-indicated in children with acute infection; any infection should be treated before, or when starting, cytotoxic drugs.

Infection in a child with neutropenia requires immediate broad-spectrum antibacterial treatment that covers all likely pathogens (Table 1, section 5.1). Appropriate bacteriological investigations should be conducted as soon as possible. Children taking cytotoxic drugs who have signs or symptoms of infection (or their carers) should be advised to seek prompt medical attention. All children should be investigated and treated under the supervision of an appropriate oncology or haematology specialist. Antifungal treatment (section 5.2) may be required in a child with prolonged neutropenia or fever lasting longer than 4–5 days. Chickenpox and measles can be particularly hazardous in immunocompromised children. Varicella-zoster immunoglobulin (section 14.5.2) is indicated if the child does not have immunity against varicella and has had close contact with infectious chickenpox or herpes zoster. Antiviral prophylaxis (section 5.3.2.1) can be considered in addition to varicella-zoster immunoglobulin or as an alternative if varicella-zoster immunoglobulin is inappropriate. If an immunocompromised child has come into close contact with an infectious individual with measles,

normal immunoglobulin (section 14.5.1) should be given.

For advice on the use of live vaccines in individuals with impaired immune response, see section 14.1.

Alopecia Reversible hair loss is a common complication, although it varies in degree between drugs and individual patients.

Pregnancy and reproductive function Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during the first trimester. Exclude pregnancy before treatment with cytotoxic drugs. Considerable caution is necessary if a pregnant woman presents with cancer requiring chemotherapy, and specialist advice should always be sought.

Contraceptive advice should be given to men and women before cytotoxic therapy begins (and should cover the duration of contraception required after therapy has ended).

Regimens that do not contain an alkylating drug or procarbazine may have less effect on fertility, but those with an alkylating drug or procarbazine carry the risk of causing permanent male sterility (there is no effect on potency). Pretreatment counselling and consideration of sperm storage may be appropriate. Women are less severely affected, though the span of reproductive life may be shortened by the onset of a premature menopause. No increase in fetal abnormalities or abortion rate has been recorded in patients who remain fertile after cytotoxic chemotherapy.

Long-term and delayed toxicity Cytotoxic drugs may produce specific organ-related toxicity in children (e.g. cardiotoxicity with doxorubicin or nephrotoxicity with cisplatin and ifosfamide). Manifestations of such toxicity may not appear for several months or even years after cancer treatment. Careful follow-up of survivors of childhood cancer is therefore vital; national and local guidelines have been developed to facilitate this.

Thromboembolism Venous thromboembolism can be a complication of cancer itself, but chemotherapy increases the risk.

Tumour lysis syndrome Tumour lysis syndrome occurs secondary to spontaneous or treatment related rapid destruction of malignant cells. Patients at risk of tumour lysis syndrome include those with non-Hodgkin's lymphoma (especially if high grade and bulky disease), Burkitt's lymphoma, acute lymphoblastic leukaemia and acute myeloid leukaemia (particularly if high white blood cell counts or bulky disease), and occasionally those with solid tumours. Pre-existing hyperuricaemia, dehydration and renal impairment are also predisposing factors. Features, include hyperkalaemia, hyperuricaemia, and hyperphosphataemia with hypocalcaemia; renal damage and arrhythmias can follow. Early recognition of patients at risk, and initiation of prophylaxis or therapy for tumour lysis syndrome, is essential.

Drugs for cytotoxic-induced side-effects

Hyperuricaemia

Hyperuricaemia, which may be present in high-grade lymphoma and leukaemia, can be markedly worsened by chemotherapy and is associated with acute renal failure.

Allopurinol is used routinely in children at low to moderate risk of hyperuricaemia. It should be started 24 hours before treatment; patients should be adequately hydrated (consideration should be given to omitting phosphate and potassium from hydration fluids). The dose of mercaptopurine or azathioprine should be reduced if allopurinol is given concomitantly (see Appendix 1).

Rasburicase is a recombinant urate oxidase used in children who are at high-risk of developing hyperuricaemia. It rapidly reduces plasma-uric acid concentration and may be of particular value in preventing complications following treatment of leukaemias or bulky lymphomas.

ALLOPURINOL

Cautions ensure adequate fluid intake; for hyperuricaemia associated with cancer therapy, allopurinol treatment should be started before cancer therapy; **interactions:** Appendix 1 (allopurinol)

Hepatic impairment reduce dose, monitor hepatic function

Renal impairment manufacturer advises reduce dose or increase dose interval in severe impairment; adjust dose to maintain plasma-oxipurinol concentration below 100 micromol/litre

Pregnancy toxicity not reported; manufacturer advises use only if no safer alternative and disease carries risk for mother or child

Breast-feeding present in milk—not known to be harmful

Side-effects rashes (withdraw therapy; if rash mild re-introduce cautiously but **discontinue** immediately if recurrence—hypersensitivity reactions occur rarely and include exfoliation, fever, lymphadenopathy, arthralgia, and eosinophilia resembling Stevens-Johnson or toxic epidermal necrolysis, vasculitis, hepatitis, renal impairment, and *very rarely* seizures); gastro-intestinal disorders; *rarely* malaise, headache, vertigo, drowsiness, visual and taste disturbances, hypertension, alopecia, hepatotoxicity, paraesthesia and neuropathy, blood disorders (including leucopenia, thrombocytopenia, haemolytic anaemia and aplastic anaemia)

Indications and dose

Prophylaxis of hyperuricaemia associated with cancer chemotherapy, prophylaxis of hyperuricaemic nephropathy, enzyme disorders causing increased serum urate e.g. Lesch-Nyhan syndrome

• By mouth

Child 1 month–15 years 10–20 mg/kg daily (max. 400 mg daily), preferably after food

Child 15–18 years initially 100 mg daily, increased according to response; max. 900 mg daily (doses over 300 mg daily given in divided doses); preferably after food

Allopurinol (Non-proprietary) (PoM)

Tablets, allopurinol 100 mg, net price 28-tab pack = 97p; 300 mg, 28-tab pack = £1.00. Label: 8, 21, 27
Brands include Caplenal®, Cosuric®, Rimapurinol®

Zyloric® (Aspen) (PoM)

Tablets, allopurinol 100 mg, net price 100-tab pack = £10.19; 300 mg, 28-tab pack = £7.31. Label: 8, 21, 27

RASBURICASE

Cautions monitor closely for hypersensitivity; atopic allergies; may interfere with test for uric acid—consult product literature

Contra-indications G6PD deficiency (section 9.1.5)

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects fever; nausea, vomiting; less frequently diarrhoea, headache, hypersensitivity reactions (including rash, bronchospasm and anaphylaxis); haemolytic anaemia, methaemoglobinaemia

Licensed use not licensed for use in children

Indications and dose

Prophylaxis and treatment of acute hyperuricaemia with initial chemotherapy for haematological malignancy

• By intravenous infusion

Consult local treatment protocol for details

Fasturtec® (Sanofi-Aventis) (PoM)

Intravenous infusion, powder for reconstitution, rasburicase, net price 1.5-mg vial (with solvent) = £69.46; 7.5-mg vial (with solvent) = £289.44

Methotrexate-induced mucositis and myelosuppression

Folinic acid (given as calcium folinate) is used to counteract the folate-antagonist action of methotrexate and thus speed recovery from methotrexate-induced mucositis or myelosuppression ('folinic acid rescue').

The calcium salt of **levofolinic acid**, a single isomer of folinic acid, is also used following methotrexate administration. The dose of calcium levofolinate is generally half that of calcium folinate.

The disodium salts of folinic acid and levofolinic acid are also used for rescue therapy following methotrexate administration.

The efficacy of high dose methotrexate is enhanced by delaying initiation of folinic acid for at least 24 hours, local protocols define the correct time. Folinic acid is normally continued until the plasma-methotrexate concentration falls to 45–90 nanograms/mL (100–200 nanomol/litre).

In the treatment of methotrexate overdose, folinate should be administered immediately; other measures to enhance the elimination of methotrexate are also necessary.

FOLINIC ACID

Cautions avoid simultaneous administration of methotrexate; **not** indicated for pernicious anaemia or other megaloblastic anaemias due to vitamin B₁₂ deficiency; **interactions:** Appendix 1 (folates)

Contra-indications

Safe Practice

Intrathecal injection **contra-indicated**

Pregnancy not known to be harmful; benefit outweighs risk

Breast-feeding presence in milk unknown but benefit outweighs risk

Side-effects rarely pyrexia after parenteral use; gastro-intestinal disturbances, insomnia, agitation, and depression after high doses

Licensed use consult product literature for licensing status of individual preparations

Indications and dose

See under preparation

Calcium folinate

(Calcium leucovorin)

Calcium Folate (Non-proprietary) (PoM)

Tablets, scored, folic acid (as calcium salt) 15 mg, net price 10-tab pack = £47.22, 30-tab pack = £85.74

Brands include *Refolinon*®

Note Not all strengths and pack sizes are available from all manufacturers

Injection, folic acid (as calcium salt) 3 mg/mL, net price 1-mL amp = £4.00, 10-mL amp = £4.62; 7.5 mg/mL, net price 2-mL amp = £7.80; 10 mg/mL, net price 5-mL vial = £19.41, 10-mL vial = £34.94, 30-mL vial = £89.95, 35-mL vial = £90.98

Brands include *Refolinon*®

Note Not all strengths and pack sizes are available from all manufacturers

Injection, powder for reconstitution, folic acid (as calcium salt), net price 15-mg vial = £4.46; 30-mg vial = £8.36

Dose

Reduction of methotrexate-induced toxicity

- By mouth, by intravenous injection or by intravenous infusion
- See notes above. Consult local treatment protocol for details

Methotrexate overdose

- By intravenous injection or by intravenous infusion
- See notes above. Consult local treatment protocol for details

Megaloblastic anaemia due to folate deficiency

- By mouth
- Child up to 12 years** 250 microgram/kg once daily
Child 12–18 years 15 mg once daily

Metabolic disorders leading to folate deficiency

- By mouth or by intravenous infusion
- Child up to 18 years** 15 mg once daily; larger doses may be required in older children

Prevention of megaloblastic anaemia associated with pyrimethamine and sulfadiazine treatment of congenital toxoplasmosis

- By mouth
- Neonate** 5 mg 3 times a week (increased up to 20 mg 3 times a week if neutropenic)
Child 1 month–1 year 10 mg 3 times a week

Disodium folinate

Sodiofolin® (Medac) (PoM)

Injection, folic acid (as disodium salt) 50 mg/mL, net price 2-mL vial = £35.09, 8-mL vial = £126.25

Dose

Antidote to methotrexate

- By intravenous injection or by intravenous infusion
- Consult local treatment protocols for details

LEVOFOLINIC ACID

Note Levofolinic acid is an isomer of folic acid

Cautions see Folic acid

Contra-indications

Safe Practice

Intrathecal injection **contra-indicated**

Pregnancy see Folic acid

Breast-feeding see Folic acid

Side-effects see Folic acid

Indications and dose

Reduction of methotrexate-induced toxicity

- By intramuscular injection or by intravenous injection or by intravenous infusion
- See notes above. Consult local treatment protocol for details

Methotrexate overdose

- By intramuscular injection or by intravenous injection or by intravenous infusion
- See notes above. Consult local treatment protocol for details

Calcium levofolinate

(Calcium levoleucovorin)

Calcium Levofolinate (Non-proprietary)

Injection, levofolinic acid (as calcium salt) 10 mg/mL, net price 17.5-mL vial = £84.63

Isovorin® (Pfizer) (PoM)

Injection, levofolinic acid (as calcium salt) 10 mg/mL, net price 2.5-mL vial = £11.62, 17.5-mL vial = £81.33

Disodium levofolinate

Levofolinic Acid (Non-proprietary) (PoM)

Injection, levofolinic acid (as disodium salt) 50 mg/mL, net price 1-mL vial = £24.70, 4-mL vial = £80.40

Urothelial toxicity

Haemorrhagic cystitis is a common manifestation of urothelial toxicity which occurs with the oxazaphosphorines, cyclophosphamide and ifosfamide; it is caused by the metabolite acrolein. Adequate hydration is essential to reduce the risk of urothelial toxicity. **Mesna** reacts specifically with acrolein in the urinary tract, preventing toxicity. Mesna is given for the same duration as cyclophosphamide or ifosfamide. It is generally given intravenously; the dose of mesna is equal to or greater than that of the oxazaphosphorine. For the role of nebulised mesna as a mucolytic in cystic fibrosis, see section 3.7.

MESNA

Contra-indications hypersensitivity to thiol-containing compounds

Pregnancy not known to be harmful

Side-effects nausea, vomiting, colic, diarrhoea, fatigue, headache, limb and joint pains, depression, irritability, rash, hypotension and tachycardia; rarely hypersensitivity reactions (more common in patients with auto-immune disorders)

Licensed use not licensed for use in children

Indications and dose**Urothelial toxicity following oxazaphosphorine therapy**

- By intravenous injection or by continuous intravenous infusion
See notes above. Consult local treatment protocol for details

Mucolytic in cystic fibrosis section 3.7**Mesna** (Non-proprietary) (PoM)

Tablets, f/c, mesna 400 mg, net price 10-tab pack = £42.90; 600 mg, 10-tab pack = £61.10

Injection, mesna 100 mg/mL, net price 4-mL amp = £3.95; 10-mL amp = £9.77

Note For oral administration contents of ampoule are taken in a flavoured drink such as orange juice or cola which may be stored in a refrigerator for up to 24 hours in a sealed container

8.1.1 Alkylating drugs

Extensive experience is available with these drugs, which are among the most widely used in cancer chemotherapy. They act by damaging DNA, thus interfering with cell replication. In addition to the side-effects common to many cytotoxic drugs (section 8.1), problems associated specifically with alkylating drugs include:

- an adverse effect on gametogenesis which may be reversible, particularly in females; amenorrhoea may also occur, which also may be reversible;
- a marked increase in the incidence of secondary tumours and leukaemia, particularly when alkylating drugs are combined with extensive irradiation;
- fluid retention with oedema and dilutional hyponatraemia in younger children; the risk of this complication is higher in the first 2 days and also when given with concomitant vinca alkaloids;
- urothelial toxicity with intravenous use; adequate hydration may reduce this risk; mesna (section 8.1) provides further protection against urotoxic effects of cyclophosphamide and ifosfamide.

BUSULFAN
(Busulphan)

Cautions see section 8.1 and notes above; monitor full blood count regularly throughout treatment; monitor cardiac and liver function; ineffective once in blast crisis phase; high dose or history of seizures—anti-epileptic prophylaxis required; previous radiation therapy, three or more cycles of chemotherapy, or previous progenitor cell transplant—increased risk of hepatic veno-occlusive disease; discontinue if lung toxicity develops; risk of second malignancy; avoid in acute porphyria (but see section 9.8.2); **interactions:** Appendix 1 (busulfan)

Hepatic impairment manufacturer advises caution and regular liver function tests—consult product literature

Pregnancy avoid (teratogenic in *animals*); manufacturers advise effective contraception during and for 6 months after treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; also hepatotoxicity (including hepatic veno-occlusive disease, hyperbilirubinaemia, jaundice, and fibrosis); cardiac tamponade in thalassaemia; pneumonia, skin hyperpigmentation; *rarely* progressive pulmonary fibrosis, seizures, aplastic anaemia, visual disturbances, hypersensitivity reactions (including urticaria, erythema); *very rarely* myasthenia gravis, gynaecomastia

Indications and dose**Conditioning treatment before haematopoietic stem-cell transplantation**

- By mouth or by intravenous infusion
Consult local treatment protocol for details

Myleran[®] (Alkopharma) (PoM)

Tablets, f/c, busulfan 2 mg, net price 25-tab pack = £65.22

Busilvex[®] (Fabre) (PoM)

Concentrate for intravenous infusion, busulfan 6 mg/mL, net price 10-mL vial = £201.25

Busulfan

Capsules, busulfan 25 mg

Available from 'special-order' manufacturers or specialist importing companies, p. 840

CHLORAMBUCIL

Cautions see section 8.1 and notes above; monitor full blood count regularly throughout treatment; increased seizure risk in children with nephrotic syndrome or history of epilepsy; avoid in acute porphyria (but see section 9.8.2)

Hepatic impairment manufacturer advises consider dose reduction in severe impairment—limited information available

Pregnancy avoid; manufacturer advises effective contraception during treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; also *less commonly* skin rash (possible progression to Stevens-Johnson syndrome and toxic epidermal necrolysis); *rarely* seizures, hepatotoxicity and jaundice; *very rarely* irreversible bone-marrow suppression, pulmonary fibrosis, tremor, peripheral neuropathy, sterile cystitis, sterility in prepubertal and pubertal males

Licensed use not licensed for use in nephrotic syndrome

Indications and dose**Hodgkin's disease**

- By mouth
Consult local treatment protocol for details

Non-Hodgkin's lymphoma

- By mouth
Consult local treatment protocol for details

Relapsing steroid-sensitive nephrotic syndrome; initiated in specialist centres (see also section 6.3.2, p. 377)

- By mouth
Child 3 months–18 years 200 micrograms/kg once daily for 8 weeks

Leukeran® (Alkopharma) (PoM)

Tablets, f/c, brown, chlorambucil 2 mg, net price 25-tab pack = £40.51

CYCLOPHOSPHAMIDE

Cautions see section 8.1 and notes above; previous or concurrent mediastinal irradiation—risk of cardio-toxicity; diabetes mellitus; avoid in acute porphyria (but see section 9.8.2); **interactions:** Appendix 1 (cyclophosphamide)

Contra-indications haemorrhagic cystitis

Hepatic impairment reduce dose—consult local treatment protocol for details

Renal impairment reduce dose—consult local treatment protocol for details

Pregnancy avoid; manufacturer advises effective contraception during and for at least 3 months after treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding during and for 36 hours after stopping treatment

Side-effects see section 8.1 and notes above; *also* anorexia; pancreatitis; cardiotoxicity at high doses; interstitial pulmonary fibrosis; inappropriate secretion of anti-diuretic hormone, disturbances of carbohydrate metabolism; urothelial toxicity; pigmentation of palms, nails and soles; *rarely* hepatotoxicity and renal dysfunction

Licensed use not licensed for use in children

Indications and dose

Acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, retinoblastoma, neuroblastoma, rhabdomyosarcoma, soft-tissue sarcomas, Ewing tumour, neuroectodermal tumours (including medulloblastoma), infant brain tumours, ependymoma, high-dose conditioning for bone marrow transplantation, lupus nephritis

- By mouth or by intravenous infusion
Consult local treatment protocol for details

Steroid-sensitive nephrotic syndrome see also section 6.3.2, p. 377

- By mouth
Child 3 months–18 years 2–3 mg/kg once daily for 8 weeks
- By intravenous infusion
Child 3 months–18 years 500 mg/m² once a month for 6 months

Administration Consult local treatment protocol for details

Cyclophosphamide (Non-proprietary) (PoM)

Tablets, s/c, cyclophosphamide (anhydrous) 50 mg, net price 100 = £70.70. Label: 25, 27

Injection, powder for reconstitution, cyclophosphamide, net price 500-mg vial = £9.20; 1-g vial = £17.06

IFOSFAMIDE

Cautions see section 8.1 and notes above; ensure satisfactory electrolyte balance, and renal function before each course (risk of tubular dysfunction, Fanconi's syndrome, or diabetes insipidus if renal toxicity not treated promptly); avoid in acute porphyria (but

see section 9.8.2); **interactions:** Appendix 1 (ifosfamide)

Contra-indications urinary tract obstruction; acute infection (including urinary-tract infection); urothelial damage

Hepatic impairment avoid

Renal impairment avoid

Pregnancy avoid (teratogenic and carcinogenic in animals); manufacturer advises adequate contraception during and for at least 6 months after treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; *also* drowsiness, confusion, disorientation, restlessness, psychosis; urothelial toxicity causing haemorrhagic cystitis and dysuria, renal toxicity (see Cautions above); *less commonly* severe encephalopathy; *rarely* diarrhoea, constipation, convulsions, anorexia; *very rarely* jaundice, thrombophlebitis, syndrome of inappropriate antidiuretic hormone secretion

Indications and dose

Rhabdomyosarcoma, soft-tissue sarcomas, Ewing tumour, germ cell tumour, osteogenic sarcoma

- By intravenous infusion
Consult local treatment protocol for details

Ifosfamide (Non-proprietary) (PoM)

Injection, powder for reconstitution, ifosfamide, net price 1-g vial = £66.08; 2-g vial = £130.04 (hosp. only)

MELPHALAN

Cautions see section 8.1 and notes above; monitor full blood count before and throughout treatment; for high-dose intravenous administration establish adequate hydration (see notes above), consider use of prophylactic anti-infective agents; haematopoietic stem cell transplantation essential for high dose treatment (consult local treatment protocol for details); avoid in acute porphyria (but see section 9.8.2); **interactions:** Appendix 1 (melphalan)

Renal impairment reduce dose initially—consult product literature

Pregnancy avoid; manufacturer advises adequate contraception during treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above

Licensed use childhood neuroblastoma

Indications and dose

High intravenous dose with haematopoietic stem cell transplantation in the treatment of childhood neuroblastoma and some other advanced embryonal tumours

- Intravenous infusion
Consult local treatment protocol for details

Alkeran® (Genopharm) (PoM)

Injection, powder for reconstitution, melphalan 50 mg (as hydrochloride). Net price 50-mg vial (with solvent-diluent) = £129.81

THIOTEPA

Cautions see section 8.1; avoid in acute porphyria (but see section 9.8.2); **interactions:** Appendix 1 (thiotepa)

Pregnancy avoid (teratogenic and embryotoxic in animals); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1

Indications and dose

Conditioning treatment before haematopoietic stem cell transplantation in the treatment of haematological disease or solid tumours, in combination with other chemotherapy

- By intravenous infusion

Consult local treatment protocol for details

Tepadina® (Adienne) [PoM]

Injection, powder for reconstitution, thiotepa, net price 15-mg vial £123.00; 100-mg vial = £736.00

Note The *Scottish Medicines Consortium* (p. 3) has advised (June 2012) that thiotepa (*Tepadina®*) is not recommended for use within NHS Scotland in combination with other chemotherapy as conditioning treatment in children or adults with haematological disease, or solid tumours prior to haematopoietic stem cell transplantation.

8.1.2 Cytotoxic antibiotics

Cytotoxic antibiotics are widely used. Many act as radiomimetics and simultaneous use of radiotherapy should be **avoided** because it may markedly increase toxicity.

Daunorubicin, **doxorubicin**, and **epirubicin** are anthracycline antibiotics. **Mitoxantrone** (mitozantrone) is an anthracycline derivative.

All anthracycline antibiotics have been associated with varying degrees of cardiac toxicity—this may be idiosyncratic and reversible, but is commonly related to total cumulative dose and is irreversible. Cardiac function should be monitored before and at regular intervals throughout treatment and afterwards. Caution is necessary with concomitant use of cardiotoxic drugs, or drugs that reduce cardiac contractility. Anthracycline antibiotics should not normally be used in children with left ventricular dysfunction. Epirubicin and mitoxantrone are considered less toxic, and may be suitable for children who have received high cumulative doses of other anthracyclines.

BLEOMYCIN

Cautions see section 8.1; ensure monitoring of pulmonary function—investigate any shortness of breath before initiation; caution in handling—irritant to tissues

Contra-indications acute pulmonary infection or significantly reduced lung function

Renal impairment reduce dose—consult local treatment protocol for details

Pregnancy avoid (teratogenic and carcinogenic in animal studies); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1, less bone marrow suppression; anorexia; pulmonary toxicity e.g. pulmonary

fibrosis (usually dose-related and delayed); fever (directly following administration), fatigue; dermatological and mucous membrane toxicity, localised skin hyperpigmentation; rarely cardiorespiratory collapse and hyperpyrexia

Licensed use not licensed for use in children

Indications and dose

Some germ cell tumours, Hodgkin's lymphoma

- By intravenous infusion

Consult local treatment protocol for details

Bleomycin (Non-proprietary) [PoM]

Injection, powder for reconstitution, bleomycin (as sulfate), net price 15 000-unit vial = £15.56

Note To conform to the European Pharmacopoeia vials previously labelled as containing '15 units' of bleomycin are now labelled as containing 15 000 units. The amount of bleomycin in the vial has not changed.

Brands include *Bleo-Kyowa®*

DACTINOMYCIN

(Actinomycin D)

Cautions see section 8.1 and notes above; caution in handling—irritant to tissues

Hepatic impairment consider dose reduction if raised serum bilirubin or biliary obstruction; consult local treatment protocols

Pregnancy avoid (teratogenic in animal studies); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; less commonly cheilitis, dysphagia; fever, malaise, lethargy; anaemia, hypoglycaemia; myalgia; acne; rarely hepatotoxicity (possibly dose-related)

Licensed use not licensed for use in children under 12 years

Indications and dose

Wilms' tumour, childhood rhabdomyosarcoma and other soft tissue sarcomas, Ewing's sarcoma

- By intravenous injection

Consult local treatment protocol for details

Dactinomycin (Non-proprietary) [PoM]

Injection, powder for reconstitution, dactinomycin Available from 'special-order' manufacturers or specialist importing companies, see p. 840

DAUNORUBICIN

Cautions see section 8.1 and notes above; caution in handling—irritant to tissues; cardiac monitoring essential

Contra-indications myocardial insufficiency, recent myocardial infarction, severe arrhythmia; previous treatment with maximum cumulative doses of daunorubicin or other anthracycline

Hepatic impairment reduce dose according to serum bilirubin concentration—consult local treatment protocol for details; avoid in severe impairment

Renal impairment reduce dose—consult local treatment protocol for details; avoid in severe impairment

Pregnancy avoid (teratogenic and carcinogenic in animal studies), see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above, leucopenia, less commonly mucositis; cardiac

toxicity (usually 1–6 months after initiation of therapy); fever; red urine discolouration

Licensed use *DaunoXome*® not licensed for use in children

Indications and dose

Acute myelogenous leukaemia, acute lymphocytic leukaemia

- By intravenous infusion

Consult local treatment protocol for details

Daunorubicin (Non-proprietary) (PoM)

Injection, powder for reconstitution, daunorubicin (as hydrochloride), net price 20-mg vial = £55.00

■ Lipid formulation

DaunoXome® (Gilead) (PoM)

Concentrate for intravenous infusion, daunorubicin encapsulated in liposomes. For dilution before use, net price 50-mg vial = £131.75

DOXORUBICIN HYDROCHLORIDE

Cautions see section 8.1 and notes above; caution in handling—irritant to tissues; **interactions:** Appendix 1 (doxorubicin)

Contra-indications severe myocardial insufficiency, recent myocardial infarction, severe arrhythmia; previous treatment with maximum cumulative doses of doxorubicin or other anthracycline

Hepatic impairment reduce dose according to bilirubin concentration—consult local treatment protocol for details; avoid in severe impairment

Pregnancy avoid (teratogenic and toxic in *animal* studies); manufacturer of liposomal product advises effective contraception during and for at least 6 months after treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; red urine discoloration; thrombophlebitis over injection site; less commonly bronchospasm, fever, amenorrhoea, and skin rash

Licensed use not licensed for use in children

Indications and dose

Paediatric malignancies including Ewing's sarcoma, osteogenic sarcoma, Wilms' tumour, neuroblastoma, retinoblastoma, some liver tumours, acute lymphoblastic leukaemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma

- By intravenous infusion

Consult local treatment protocol for details

Doxorubicin (Non-proprietary) (PoM)

Injection, powder for reconstitution, doxorubicin hydrochloride, net price 10-mg vial = £18.72; 50-mg vial = £100.12

Injection, doxorubicin hydrochloride 2 mg/mL, net price 5-mL vial = £18.54, 25-mL vial = £92.70, 100-mL vial = £370.80

EPIRUBICIN HYDROCHLORIDE

Cautions see section 8.1 and notes above; caution in handling—irritant to tissues

Contra-indications severe myocardial insufficiency, recent myocardial infarction, severe arrhythmia, unstable angina, myocardiopathy; previous treatment

with maximum cumulative doses of epirubicin or other anthracycline

Hepatic impairment reduce dose according to bilirubin concentration—consult local treatment protocol for details; avoid in severe impairment

Renal impairment dose reduction may be necessary in severe impairment

Pregnancy avoid (carcinogenic in *animal* studies); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; red urine discoloration; anaphylaxis

Licensed use not licensed for use in children

Indications and dose

Recurrent acute lymphoblastic leukaemia, rhabdomyosarcoma, other soft tissue tumours of childhood

- Intravenous infusion

Consult local treatment protocol for details

Epirubicin hydrochloride (Non-proprietary) (PoM)

Injection, epirubicin hydrochloride 2 mg/mL, net price 5-mL vial = £17.38, 25-mL vial = £84.85, 50-mL vial = £95.54, 100-mL vial = £306.20

Injection, powder for reconstitution, epirubicin hydrochloride, net price 50-mg vial = £91.54

Pharmorubicin® **Solution for Injection**

(Pharmacia) (PoM)

Injection, epirubicin hydrochloride 2 mg/mL, net price 5-mL vial = £21.24, 25-mL vial = £106.19, 100-mL vial = £386.16

MITOXANTRONE

(Mitoxantrone)

Cautions see section 8.1 and notes above

Hepatic impairment use with caution—consult local treatment protocol

Pregnancy avoid; effective contraception during and for at least 6 months after treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; transient blue-green discoloration of urine; less commonly gastro-intestinal bleeding, anorexia, allergic reactions, dyspnoea, fatigue, fever, amenorrhoea, and transient blue discoloration of skin and nails

Licensed use not licensed for use in children

Indications and dose

Acute myeloid leukaemia, recurrent acute lymphoblastic leukaemia

- By intravenous infusion

Consult local treatment protocol for details

Mitoxantrone (Non-proprietary) (PoM)

Concentrate for intravenous infusion, mitoxantrone (as hydrochloride) 2 mg/mL, net price 10-mL vial = £100.00

Onkotrone® (Baxter) (PoM)

Concentrate for intravenous infusion, mitoxantrone (as hydrochloride) 2 mg/mL, net price 10-mL vial = £121.85, 12.5-mL vial = £152.33, 15-mL vial = £203.04

8.1.3 Antimetabolites

Antimetabolites are incorporated into new nuclear material or they combine irreversibly with cellular enzymes and prevent normal cellular division. **Cytarabine**, **fludarabine**, **mercaptopurine**, **methotrexate**, and **tioguanine** are commonly used in paediatric chemotherapy.

Methotrexate inhibits the enzyme dihydrofolate reductase, essential for the synthesis of purines and pyrimidines. It is given by mouth, intravenously, intramuscularly, or intrathecally. Methotrexate causes myelosuppression, mucositis, and rarely pneumonitis. It is **contra-indicated** in significant renal impairment because it is excreted primarily by the kidney. It is also contra-indicated in patients with severe hepatic impairment. It should also be **avoided** in the presence of significant pleural effusion or ascites because it can accumulate in these fluids, and its subsequent return to the circulation may cause myelosuppression. Systemic toxicity may follow intrathecal administration and blood counts should be carefully monitored. Folinic acid (section 8.1) following methotrexate administration helps to prevent methotrexate-induced mucositis and myelosuppression.

Cytarabine acts by interfering with pyrimidine synthesis. It is given subcutaneously, intravenously, or intrathecally. It is a potent myelosuppressant and requires careful haematological monitoring. A liposomal formulation of cytarabine for intrathecal use is available for lymphomatous meningitis.

Fludarabine is generally well tolerated but does cause myelosuppression, which may be cumulative.

Fludarabine has a potent and prolonged immunosuppressive effect. Children treated with fludarabine are more prone to serious bacterial, opportunistic fungal, and viral infections, and prophylactic therapy is recommended in children at risk. To prevent potentially fatal transfusion-related graft-versus-host reaction, only irradiated blood products should be administered. Prescribers should consult specialist literature when using highly immunosuppressive drugs.

Clofarabine is licensed for the treatment of acute lymphoblastic leukaemia in children who have relapsed or are refractory after receiving at least two previous regimens. It is given by intravenous infusion.

Nelarabine is licensed for the treatment of T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma in children who have relapsed or who are refractory after receiving at least two previous regimens. It is given by intravenous infusion. Neurotoxicity is common with nelarabine, and close monitoring for neurological events is strongly recommended—discontinue treatment if neurotoxicity occurs.

Mercaptopurine is used as maintenance therapy for acute lymphoblastic leukaemia and in the management of ulcerative colitis and Crohn's disease (section 1.5). Azathioprine, which is metabolised to mercaptopurine, is generally used as an immunosuppressant (section 8.2.1 and section 10.1.3). The dose of both drugs should be reduced if the child is receiving allopurinol since it interferes with their metabolism. For the role of thio-

purine methyltransferase (TPMT) in the metabolism of azathioprine see section 8.2.1.

Tioguanine (thioguanine) is given by mouth for the treatment of acute lymphoblastic leukaemia; it is given at various stages of treatment in short-term cycles. Tioguanine has a lower incidence of gastro-intestinal side-effects than mercaptopurine. Long-term therapy with tioguanine is not recommended because of the high risk of liver toxicity.

CLOFARABINE

Cautions see section 8.1; cardiac disease

Hepatic impairment manufacturer advises caution in mild to moderate impairment; avoid in severe impairment

Renal impairment manufacturer advises caution in mild to moderate impairment; avoid in severe impairment

Pregnancy manufacturer advises avoid (teratogenic in animal studies); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1; also diarrhoea, abdominal pain, jaundice; tachycardia, flushing, hypotension, pericardial effusion, oedema, haematoma; dyspnoea, cough; anxiety, agitation, dizziness, drowsiness, headache, paraesthesia, peripheral neuropathy, restlessness; haematuria; arthralgia, myalgia; rash, pruritus, hand-foot (desquamative) syndrome, increased sweating; pancreatitis also reported

Licensed use not licensed for use in children under 1 year

Indications and dose

Relapsed or refractory acute lymphoblastic leukaemia

- By intravenous infusion

Consult local treatment protocol for details

Evoltra® (Sanofi-Aventis) ▼ (POM)

Concentrate for intravenous infusion, clofarabine
1 mg/mL, net price 20-mL vial = £1326.18

Electrolytes Na⁺ 3.08 mmol/vial

CYTARABINE

Cautions see section 8.1 and notes above; **interactions**: Appendix 1 (cytarabine)

Hepatic impairment reduce dose—consult product literature

Renal impairment consult local treatment protocols

Pregnancy avoid (teratogenic in animal studies); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; 'cytarabine syndrome'—6–12 hours after intravenous administration—characterised by fever and malaise, myalgia, bone pain, maculopapular rash, and occasionally chest pain; *less commonly* conjunctivitis (consider prophylactic corticosteroid eye drops), neurotoxicity, renal and hepatic dysfunction, jaundice; *rarely* severe spinal cord toxicity following intrathecal administration

Licensed use **Depocyte**® intrathecal injection not licensed for use in children

Indications and dose**Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin's lymphoma**

- By intravenous injection, by intravenous infusion, or by subcutaneous injection

Consult local treatment protocol for details

Meningeal leukaemia, meningeal neoplasms

- By intrathecal injection

Consult local treatment protocol for details

Note

Based on weight or body-surface area, children may tolerate higher doses of cytarabine than adults

Cytarabine (Non-proprietary) (PoM)

Injection (for intravenous, subcutaneous or intrathecal use), cytarabine 20 mg/mL, net price 5-mL vial = £3.90

Injection (for intravenous or subcutaneous use), cytarabine 20 mg/mL, net price 5-mL vial = £3.90, 25-mL vial = £19.50

Injection (for intravenous or subcutaneous use), cytarabine 100 mg/mL, net price 1-mL vial = £6.00; 5-mL vial = £20.00; 10-mL vial = £39.00; 20-mL vial = £77.50

▲Lipid formulation for intrathecal use**DepoCyt[®]** (Napp) (PoM)

Intrathecal injection, cytarabine encapsulated in liposomes, net price 50-mg vial = £1223.75

FLUDARABINE PHOSPHATE

Cautions see section 8.1 and notes above; monitor for signs of haemolysis; monitor for neurological toxicity; worsening of existing and increased susceptibility to skin cancer; **interactions:** Appendix 1 (fludarabine)

Contra-indications haemolytic anaemia

Renal impairment reduce dose by up to 50% if creatinine clearance 30–70 mL/minute/1.73 m²; avoid if creatinine clearance less than 30 mL/minute/1.73 m²

Pregnancy avoid (embryotoxic and teratogenic in animal studies); manufacturer advises effective contraception during and for at least 6 months after treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; also diarrhoea, anorexia, oedema, pneumonia, cough, peripheral neuropathy, chills, fever, malaise, weakness, myelodysplastic syndrome, acute myeloid leukaemia, visual disturbances, rash; *less commonly* pulmonary toxicity (including pneumonitis and fibrosis), confusion, haemorrhage, autoimmune disorder; *rarely* heart failure, arrhythmia, coma, seizures, agitation, skin cancer, optic neuropathy, blindness, Stevens-Johnson syndrome, toxic epidermal necrolysis; *also reported* haemorrhagic cystitis

Licensed use not licensed for use in children

Indications and dose

Poor prognosis or relapsed acute myeloid leukaemia, relapsed acute lymphoblastic leukaemia, conditioning before bone marrow transplantation

- By mouth, by intravenous injection, or by intravenous infusion

Consult local treatment protocol for details

Fludarabine phosphate (Non-proprietary) (PoM)

Injection, powder for reconstitution, fludarabine phosphate, net price 50-mg vial = £155.00

Concentrate for intravenous injection or infusion, fludarabine phosphate 25 mg/mL, net price 2-mL vial = £155.00

Note Must be diluted before administration (consult product literature)

Fludara[®] (Sanofi-Aventis) (PoM)

Tablets, f/c, pink, fludarabine phosphate 10 mg, net price 15-tab pack = £302.48, 20-tab pack = £403.31

Injection, powder for reconstitution, fludarabine phosphate, net price 50-mg vial = £147.07

MERCAPTOPURINE

(6-Mercaptopurine)

Cautions see section 8.1 and notes above; thiopurine methyltransferase status (see section 8.2.1); monitor liver function—discontinue if jaundice develops; **interactions:** Appendix 1 (mercaptopurine)

Hepatic impairment may need dose reduction

Renal impairment manufacturer advises consider reducing dose

Pregnancy avoid (teratogenic); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; gastrointestinal effects less common; hepatotoxicity (more frequent at higher doses); *rarely* intestinal ulceration, pancreatitis, fever, crystalluria with haematuria, rash, and hyperpigmentation; *very rarely* lymphoma

Licensed use not licensed for use in children for acute lymphoblastic lymphoma or T-cell non-Hodgkins lymphoma

Indications and dose

Acute lymphoblastic leukaemia, lymphoblastic lymphomas

- By mouth

Consult local treatment protocol for details

Severe ulcerative colitis and Crohn's disease section 1.5.3

Important *Puri-Nethol[®]* tablets and *Xaluprine[®]* oral suspension are not bioequivalent, haematological monitoring is advised when switching formulations

Puri-Nethol[®] (Alkopharma) (PoM)

Tablets, yellow, scored, mercaptopurine 50 mg, net price 25-tab pack = £50.47

Xaluprine[®] (Nova) (PoM)

Oral Suspension, mercaptopurine, 20 mg/mL, net price 100 mL (raspberry-flavoured) = £170.00

Excipients include aspartame (section 9.4.1)

Mercaptopurine

Capsules, mercaptopurine 10 mg

Available from 'special-order' manufacturers or specialist importing companies, p. 840

METHOTREXATE

Cautions see section 8.1 and section 10.1.3; monitor renal and hepatic function; peptic ulceration, ulcerative colitis, diarrhoea, and ulcerative stomatitis; porphyria (section 9.8.2); **interactions:** Appendix 1 (methotrexate)

Hepatic impairment avoid in severe impairment—consult local treatment protocol for details

Renal impairment reduce dose—risk of nephrotoxicity at high doses; avoid in severe impairment

Pregnancy avoid (teratogenic; fertility may be reduced during therapy but this may be reversible); manufacturer advises effective contraception during and for at least 3 months after treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding—present in milk

Side-effects see section 8.1; also anorexia, abdominal discomfort, dyspepsia, gastro-intestinal ulceration and bleeding, diarrhoea, toxic megacolon, hepatotoxicity (see Cautions above); hypotension, pericarditis, pericardial tamponade, thrombosis; pulmonary oedema, pleuritic pain, pulmonary fibrosis, interstitial pneumonitis (see also Pulmonary Toxicity, p. 513); anaphylactic reactions, urticaria; dizziness, chills, fever, drowsiness, insomnia, malaise, headache, mood changes, abnormal cranial sensations, neurotoxicity, confusion, psychosis, paraesthesia, cerebral oedema; precipitation of diabetes; menstrual disturbances, vaginitis, cystitis, reduced libido, impotence; haematuria, dysuria, renal failure; osteoporosis, arthralgia, myalgia, vasculitis; conjunctivitis, blepharitis, visual disturbances; rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, changes in nail and skin pigmentation, telangiectasia, acne, furunculosis, ecchymosis; injection-site reactions

Indications and dose

Maintenance and remission of acute lymphoblastic leukaemia, lymphoblastic lymphoma

- By mouth

Consult local treatment protocol for details

Treatment of early stage Burkitt's lymphoma, non-Hodgkin's lymphoma, osteogenic sarcoma, some CNS tumours including infant brain tumours, acute lymphoblastic leukaemia

- By intravenous injection or infusion

Consult local treatment protocol for details

Meningeal leukaemia, treatment and prevention of CNS involvement of leukaemia

- By intrathecal injection

Consult local treatment protocol for details

Severe Crohn's disease section 1.5.3

Rheumatic disease section 10.1.3

Psoriasis section 13.5.3

Metothrexate (Non-proprietary) (PoM)

Injection, methotrexate (as sodium salt) 2.5 mg/mL, net price 2-mL vial = £4.80

Injection, methotrexate (as sodium salt) 25 mg/mL, net price 2-mL vial = £2.62, 20-mL vial = £25.07

Injection, methotrexate 100 mg/mL (not for intrathecal use), net price 10-mL vial = £78.00, 50-mL vial = £380.00

Oral preparations

Section 10.1.3

NELARABINE

Cautions see section 8.1 and notes above; previous or concurrent intrathecal chemotherapy or craniospinal irradiation (increased risk of neurotoxicity)

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. cycling or driving)

Pregnancy avoid (teratogenic in *animal* studies); manufacturer advises effective contraception during and for at least 3 months after treatment in men and women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; also constipation, diarrhoea; confusion, seizures, drowsiness, peripheral neurological disorders, demyelination, hypoesthesia, paraesthesia, ataxia, tremor, headache, asthenia, fatigue; pyrexia; hypoglycaemia, electrolyte disturbances; arthralgia; benign and malignant tumours also reported

Indications and dose

T-cell acute lymphoblastic leukaemia, T-cell lymphoblastic lymphoma

- By intravenous infusion

Consult local treatment protocol for details

Atriance® (GSK) (PoM)

Intravenous infusion, nelarabine 5 mg/mL, net price 50-mL vial = £222.00

Electrolytes Na⁺ 3.75 mmol/vial

TIOGUANINE

(Thioguanine)

Cautions see section 8.1 and notes above; thiopurine methyltransferase status (see section 8.2.1); monitor liver function weekly—discontinue if liver toxicity develops; **interactions:** Appendix 1 (thioguanine)

Hepatic impairment reduce dose

Renal impairment reduce dose

Pregnancy avoid (teratogenicity reported when men receiving thioguanine have fathered children); ensure effective contraception during treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1; also stomatitis and hepatotoxicity; rarely intestinal necrosis and perforation

Indications and dose

Infant acute lymphoblastic leukaemia

- By mouth

Consult local treatment protocol for details

Lanvis® (Alkopharma) (PoM)

Tablets, yellow, scored, thioguanine 40 mg, net price 25-tab pack = £103.54

8.1.4 Vinca alkaloids and etoposide

The vinca alkaloids, **vinblastine** and **vincristine** are used to treat a variety of cancers including leukaemias, lymphomas, and some solid tumours.

Neurotoxicity, usually as peripheral or autonomic neuropathy, occurs with all vinca alkaloids and is a

limiting side-effect of vincristine; it occurs less often with vinblastine. Children with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; ototoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced, but children generally tolerate vincristine better than adults. Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.

Myelosuppression is the dose-limiting side-effect of vinblastine; vincristine causes negligible myelosuppression. The vinca alkaloids may cause reversible alopecia. They cause severe local irritation and care must be taken to avoid extravasation. Constipation is common with vinblastine and vincristine; prophylactic use of laxatives may be considered.

Safe Practice

Vinblastine and vincristine are for **intravenous administration only**. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that teenage patients treated in an adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

Etoposide, usually given by slow intravenous infusion, is used to treat acute leukaemias, lymphomas, and some solid tumours. Etoposide may also be given by mouth but it is unpredictably absorbed.

ETOPOSIDE

Cautions see section 8.1 and notes above; **interactions:** Appendix 1 (etoposide)

Hepatic impairment avoid in severe impairment

Renal impairment consider dose reduction—consult local treatment protocol for details

Pregnancy avoid (teratogenic in *animal* studies); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1, dose limiting myelosuppression, mucositis more common if given with doxorubicin; anaphylaxis associated with concentrated infusions; hypotension associated with rapid infusion; irritant to tissues if extravasated

Licensed use not licensed for use in children

Indications and dose

Stage 4 neuroblastoma, germ-cell tumours, intracranial germ-cell tumours, rhabdomyosarcoma, soft-tissue sarcomas, neuroectodermal tumours (including medulloblastoma), relapsed Hodgkin's disease, non-Hodgkin's lymphoma, Ewing tumour, acute lymphoblastic leukaemia, acute myeloid leukaemia

- By mouth or by intravenous infusion

Consult local treatment protocol for details

Etoposide (Non-proprietary) (PoM)

Concentrate for intravenous infusion, etoposide 20 mg/mL, net price 5-mL vial = £12.15, 10-mL vial = £29.00, 25-mL vial = £60.75

Brands include Eposin®

Etopophos® (Bristol-Myers Squibb) (PoM)

Injection, powder for reconstitution, etoposide (as phosphate), net price 100-mg vial = £26.17 (hosp. only)

Vepesid® (Bristol-Myers Squibb) (PoM)

Capsules, both pink, etoposide 50 mg, net price 20 = £99.82; 100 mg, 10-cap pack = £87.23 (hosp. only). Label: 23

VINBLASTINE SULFATE

Cautions see section 8.1 and notes above; caution in handling; **interactions:** Appendix 1 (vinblastine)

Contra-indications see notes above

Safe Practice

Intrathecal injection **contra-indicated**

Hepatic impairment dose reduction may be necessary—consult local treatment protocol for details

Pregnancy avoid (limited experience suggests fetal harm; teratogenic in *animal* studies); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; abdominal pain, constipation, leucopenia, muscle pain; less commonly peripheral neuropathy; rarely paralytic ileus; irritant to tissues if extravasated

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Hodgkin's disease and other lymphomas

- By intravenous injection

Consult local treatment protocol for details

Vinblastine (Non-proprietary) (PoM)

Injection, vinblastine sulfate 1 mg/mL, net price 10-mL vial = £13.09

Velbe® (Genus) (PoM)

Injection, powder for reconstitution, vinblastine sulfate, net price 10-mg amp = £14.15

VINCISTINE SULFATE

Cautions see section 8.1 and notes above; neuromuscular disease; ileus; caution in handling; **interactions:** Appendix 1 (vincristine)

Contra-indications see notes above

Safe Practice

Intrathecal injection **contra-indicated**

Hepatic impairment dose reduction may be necessary—consult local treatment protocol for details

Pregnancy avoid (teratogenicity and fetal loss in *animal* studies); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; constipation (see notes above), diarrhoea, intestinal necrosis, paralytic ileus may occur in young children; dose-limiting neuromuscular effects (see notes above); urinary retention, rarely convulsions followed by coma; inappropriate secretion of antidiuretic hormone; irritant to tissues if extravasated

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose**Acute leukaemias, lymphomas, paediatric solid tumours**

- By intravenous injection

Consult local treatment protocol for details

Vincristine (Non-proprietary) (PoM)

Injection, vincristine sulfate 1 mg/mL, net price
1-mL vial = £10.92; 2-mL vial = £21.17; 5-mL vial =
£44.16

Oncovin® (Genus) (PoM)

Injection, vincristine sulfate 1 mg/mL, net price
1-mL vial = £14.18; 2-mL vial = £28.05

8.1.5 Other antineoplastic drugs**Asparaginase**

Asparaginase is used almost exclusively in the treatment of acute lymphoblastic leukaemia. Hypersensitivity reactions may occur and facilities for the management of anaphylaxis should be available. A number of different preparations of asparaginase exist and only the product specified in the treatment protocol should be used.

Crisantaspase is the enzyme asparaginase produced by *Erwinia chrysanthemi*. Preparations of asparaginase derived from *Escherichia coli* are also available. Children who are hypersensitive to asparaginase derived from one organism may tolerate asparaginase derived from another organism but cross-sensitivity occurs in about 20–30% of individuals.

CRISANTASPASE**Cautions** see section 8.1 and notes above**Contra-indications** history of pancreatitis related to asparaginase therapy**Pregnancy** avoid; see also Pregnancy and Reproductive Function, p. 421**Breast-feeding** discontinue breast-feeding

Side-effects see section 8.1; also liver dysfunction, pancreatitis, diarrhoea; coagulation disorders; lethargy, drowsiness, confusion, dizziness, neurotoxicity, convulsions, headache; *less commonly* changes in blood lipids, anaphylaxis, hyperglycaemia; *rarely* CNS depression; *very rarely* myalgia; abdominal pain and hypertension also reported

Indications and dose**Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin's lymphoma**

- By intravenous, intramuscular or subcutaneous injection

Consult local treatment protocol for details

Erwinase® (EUSA Pharma) (PoM)

Injection, powder for reconstitution, crisantaspase,
net price 10 000-unit vial = £613.00

Preparations

Preparations of asparaginase derived from *Escherichia coli* are available but they are not licensed, they include: *Medac®* asparaginase, *Elspar®* asparaginase, and *Oncaspar®* pegaspargase.

Dacarbazine and temozolomide

Dacarbazine is a component of a commonly used combination for Hodgkin's disease (ABVD—doxorubicin [previously *Adriamycin®*], bleomycin, vinblastine, and dacarbazine). It is given *intravenously*.

Temozolomide is structurally related to dacarbazine and is used in children for second-line treatment of malignant glioma.

DACARBAZINE**Cautions** see section 8.1; caution in handling**Hepatic impairment** dose reduction may be required in combined hepatic and renal impairment; avoid in severe impairment**Renal impairment** dose reduction may be required in combined renal and hepatic impairment; avoid in severe impairment**Pregnancy** avoid (carcinogenic and teratogenic in animal studies); ensure effective contraception during and for at least 6 months after treatment in men or women; see also Pregnancy and Reproductive Function, p. 421**Breast-feeding** discontinue breast-feeding

Side-effects see section 8.1; *also* anorexia; *less commonly* facial flushing, confusion, headache, seizures, facial paraesthesia, influenza-like symptoms, blurred vision, renal impairment, rash; *rarely* diarrhoea, hepatotoxicity including liver necrosis and hepatic vein thrombosis, photosensitivity, irritant to skin and tissues, injection-site reactions

Indications and dose**Hodgkin's disease, paediatric solid tumours**

- By intravenous injection or by intravenous infusion

Consult local treatment protocol for details

Dacarbazine (Non-proprietary) (PoM)

Injection, powder for reconstitution, dacarbazine (as citrate), net price 100-mg vial = £5.05; 200-mg vial = £7.50; 500-mg vial = £16.50; 600-mg vial = £22.50; 1-g vial = £31.80

TEMOZOLOMIDE

Cautions see section 8.1; *Pneumocystis jirovecii* pneumonia—consult product literature for monitoring and prophylaxis requirements; monitor liver function before treatment initiation, after each treatment cycle and midway through 42-day treatment cycles—consider the balance of benefits and risks of treatment if results are abnormal at any point (fatal liver injury reported); monitor for myelodysplastic syndrome and secondary malignancies; **interactions:** Appendix 1 (temozolomide)

Hepatic impairment use with caution in severe impairment—no information available**Renal impairment** manufacturer advises caution—no information available

Pregnancy avoid (teratogenic and embryotoxic in animal studies); manufacturer advises adequate contraception during treatment; men should avoid fathering a child during and for at least 6 months after treatment; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding**Side-effects** see section 8.1 and consult product literature

Indications and dose**Treatment of recurrent or progressive malignant glioma**

- By mouth

Consult local treatment protocol for details

Temozolomide (Non-proprietary) PoM

Capsules, temozolomide 5 mg, net price 5-cap pack = £16.00; 20 mg, 5-cap pack = £60.30; 100 mg, 5-cap pack = £320.80; 140 mg, 5-cap pack = £451.40; 180 mg, 5-cap pack = £580.37; 250 mg, 5-cap pack = £806.08. Label: 23, 25

Brands include *Temomedac*®

Temodal® (MSD) PoM

Capsules, temozolomide 5 mg (green/white), net price 5-cap pack = £10.59; 20 mg (yellow/white), 5-cap pack = £42.35; 100 mg (pink/white), 5-cap pack = £211.77; 140 mg (blue/white), 5-cap pack = £296.48; 180 mg (orange/white), 5-cap pack = £381.19; 250 mg (white), 5-cap pack = £529.43. Label: 23, 25

Mitotane

Mitotane is used in children for the symptomatic treatment of advanced or inoperable adrenocortical carcinoma. It selectively inhibits the activity of the adrenal cortex, necessitating corticosteroid replacement therapy (section 6.3.1); the dose of glucocorticoid should be increased in case of shock, trauma, or infection. Neuropsychological impairment can occur, possibly secondary to hypothyroidism, and growth retardation has also been reported in children treated with mitotane.

MITOTANE

Cautions see notes above; risk of accumulation in overweight patients; monitor plasma-mitotane concentration—consult product literature; avoid in acute porphyria (section 9.8.2); **interactions**: Appendix 1 (mitotane)

Skilled tasks Central nervous system toxicity may affect performance of skilled tasks

Counselling Children and their carers should be warned to contact doctor immediately if injury, infection, or illness occurs (because of the risk of acute adrenal insufficiency)

Hepatic impairment manufacturer advises caution in mild to moderate impairment—monitoring of plasma-mitotane concentration recommended; avoid in severe impairment

Renal impairment manufacturer advises caution in mild to moderate renal impairment—monitoring of plasma-mitotane concentration recommended; avoid in severe impairment

Pregnancy manufacturer advises avoid—women of child-bearing age should use effective contraception during and after treatment; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; also gastro-intestinal disturbances (including nausea, vomiting, diarrhoea, epigastric discomfort), anorexia, liver disorders; hypercholesterolaemia, hypertriglyceridaemia; ataxia, confusion, asthenia, myasthenia, paraesthesia, drowsiness, neuropathy, cognitive impairment, movement disorder, dizziness, headache; gynaecomastia; prolonged bleeding time, leucopenia, thrombocytopenia, anaemia; rash; *rarely* hypersalivation, hypertension, postural hypotension, flushing, pyrexia, haematuria, proteinuria, haemorrhagic cyst-

itis, hypouricaemia, visual disturbances and ocular disorders

Licensed use not licensed for use in children

Indications and dose**Symptomatic treatment of advanced or inoperable adrenocortical carcinoma**

- By mouth

Consult local treatment protocol for details

Lysodren® (HRA Pharma) PoM

Tablets, scored, mitotane 500 mg, net price 100-tab pack = £590.97. Label: 2, 10, 21, counselling, skilled tasks, adrenal suppression

Platinum compounds

Carboplatin is used in the treatment of a variety of paediatric malignancies; it is given by intravenous infusion. Carboplatin can be given in an outpatient setting and is better tolerated than cisplatin; nausea and vomiting are less severe and nephrotoxicity, neurotoxicity, and ototoxicity are much less of a problem. Carboplatin is, however, more myelosuppressive than cisplatin.

Cisplatin is of value in children with a variety of malignancies; it is given by intravenous infusion. Cisplatin requires intensive intravenous hydration; routine use of intravenous fluids containing potassium or magnesium may also be required to help control hypokalaemia and hypomagnesaemia. Treatment may be complicated by severe nausea and vomiting; delayed vomiting may occur and is difficult to control. Cisplatin has dose-related and potentially cumulative side-effects including nephrotoxicity, neurotoxicity, and ototoxicity. Baseline testing of renal function and hearing is required; for children with pre-existing renal or hearing impairment or marked bone-marrow suppression, consideration should be given to withholding treatment or using another drug.

CARBOPLATIN

Cautions see section 8.1 and notes above; consider therapeutic drug monitoring; **interactions**: Appendix 1 (platinum compounds)

Renal impairment reduce dose and monitor haematological parameters and renal function; avoid if creatinine clearance less than 20 mL/minute/1.73 m²

Pregnancy avoid (teratogenic and embryotoxic in animal studies); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above

Licensed use not licensed for use in children

Indications and dose

Stage 4 neuroblastoma, germ cell tumours, low-grade gliomas (including astrocytomas), neuroectodermal tumours (including medulloblastoma), rhabdomyosarcoma (metastatic and non-metastatic disease), soft-tissue sarcomas, retinoblastoma, high risk Wilms' tumour, some liver tumours

- By intravenous infusion

Consult local treatment protocol for details

Carboplatin (Non-proprietary) PoM

Injection, carboplatin 10 mg/mL, net price 5-mL vial = £20.00, 15-mL vial = £50.00, 45-mL vial = £160.00, 60-mL vial = £260.00

CISPLATIN

Cautions see section 8.1 and notes above; monitor full blood count, renal function, audiology, and plasma electrolytes; **interactions:** Appendix 1 (platinum compounds)

Renal impairment avoid if possible—nephrotoxic

Pregnancy avoid (teratogenic and toxic in *animal* studies); manufacturer advises effective contraception during and for at least 3 months after treatment in men or women; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; also peripheral neuropathy; hypophosphataemia, hypocalcaemia, hyperuricaemia also reported

Licensed use not licensed for use in children

Indications and dose

Osteogenic sarcoma, stage 4 neuroblastoma, some liver tumours, infant brain tumours, intracranial germ-cell tumours

- By intravenous infusion

Consult local treatment protocol for details

Cisplatin (Non-proprietary) (PoM)

Injection, cisplatin 1 mg/mL, net price 10-mL vial = £5.90, 50-mL vial = £24.50, 100-mL vial = £50.22

Injection, powder for reconstitution, cisplatin, net price 50-mg vial = £17.00

Procabazine

Procabazine is most often used in Hodgkin's disease. It is given *by mouth*. It is a weak monoamine-oxidase inhibitor and dietary restriction is rarely considered necessary. Alcohol ingestion may cause a disulfiram-like reaction.

PROCABAZINE

Cautions see section 8.1 and notes above; cardiovascular or cerebrovascular disease; pheochromocytoma; epilepsy; **interactions:** Appendix 1 (procabazine)

Contra-indications pre-existing severe leucopenia or thrombocytopenia

Hepatic impairment caution in mild to moderate impairment; avoid in severe impairment

Renal impairment caution in mild to moderate impairment; avoid in severe impairment

Pregnancy avoid (teratogenic in *animal* studies and isolated reports in humans); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; loss of appetite; also reported jaundice, hypersensitivity rash (discontinue treatment)

Indications and dose

Hodgkin's lymphoma

- By mouth

Consult local treatment protocol for details

Procabazine (Non-proprietary) (PoM)

Capsules, ivory, procabazine (as hydrochloride) 50 mg, net price 50-cap pack = £249.50. Label: 4

Protein kinase inhibitors

Everolimus, a protein kinase inhibitor, is licensed in children from the age of 3 years for the treatment of subependymal giant cell astrocytoma associated with tuberous sclerosis complex who require therapeutic intervention but are not amenable to surgery.

Imatinib, a tyrosine kinase inhibitor, is licensed in children for the treatment of newly diagnosed Philadelphia-chromosome-positive chronic myeloid leukaemia when bone marrow transplantation is not considered first line treatment, and for Philadelphia-chromosome-positive chronic myeloid leukaemia in chronic phase after failure of interferon alfa, or in accelerated phase, or in blast crisis.

EVEROLIMUS

Cautions see section 8.1; monitor blood-glucose concentration, serum-triglycerides and serum-cholesterol before treatment and periodically thereafter; concomitant use of drugs that increase risk of bleeding; history of bleeding disorders; monitor renal function before treatment and periodically thereafter; reduce dose or discontinue if severe side-effects occur—consult product literature; **interactions:** Appendix 1 (everolimus)

Pneumonitis Non-infectious pneumonitis reported.

Children and their carers should be advised to seek urgent medical advice if new or worsening respiratory symptoms occur

Hepatic impairment consult product literature

Pregnancy manufacturer advises avoid (toxicity in *animal* studies); effective contraception must be used during and for up to 8 weeks after treatment; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding manufacturer advises avoid

Side-effects see section 8.1; also diarrhoea, dry mouth, abdominal pain, dysphagia, anorexia, taste disturbance, chest pain, hypertension, hyperlipidaemia, hypercholesterolaemia, peripheral oedema, pneumonitis (including interstitial lung disease), asthenia, fatigue, headache, insomnia, convulsions, irritability, increased susceptibility to infections (including pneumonia, aspergillosis, and candidiasis), hyperglycaemia, hypoglycaemia, dehydration, renal failure, electrolyte disturbance, arthralgia, eyelid oedema, epistaxis, skin and nail disorders (including hand-foot syndrome); less commonly congestive heart failure, flushing, agitation, aggression, rhabdomyolysis and impaired wound healing; hepatitis B reactivation and haemorrhage also reported

Indications and dose

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

- By mouth

Consult product literature

Votubia® (Novartis) ▼ (PoM)

Tablets, white-yellow, everolimus, 2.5 mg, net price 30-tab pack = £1200.00; 5 mg, 30-tab pack = £2250.00; 10 mg, 30-tab pack = £2970.00. Label: 25, counselling, pneumonitis

Note *Votubia*® tablets may be dispersed in approximately 30 mL of water by gently stirring, immediately before drinking. After solution has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed

IMATINIB

Cautions see section 8.1; cardiac disease; risk factors for heart failure; history of renal failure; monitor for fluid retention; monitor liver function (see also Hepatic Impairment, below); monitor growth in children (may cause growth retardation); **interactions:** Appendix 1 (imatinib)

Hepatic impairment start with minimum recommended dose; reduce dose further if not tolerated; consult local treatment protocol

Renal impairment start with minimum recommended dose; reduce dose further if not tolerated; consult local treatment protocol

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk; effective contraception required during treatment; see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1; also abdominal pain, appetite changes, constipation, diarrhoea, flatulence, gastro-oesophageal reflux, taste disturbance, weight changes, dry mouth; oedema (including pulmonary oedema, pleural effusion, and ascites), flushing, haemorrhage; cough, dyspnoea; dizziness, headache, insomnia, hypoesthesia, paraesthesia, fatigue; influenza-like symptoms; cramps, arthralgia; visual disturbances, lacrimation, conjunctivitis, dry eyes; epistaxis; dry skin, sweating, rash, pruritus, photosensitivity; *less commonly* gastric ulceration, pancreatitis, hepatic dysfunction (rarely hepatic failure, hepatic necrosis), dysphagia, heart failure, tachycardia, palpitation, syncope, hypertension, hypotension, cold extremities, cough, acute respiratory failure, depression, drowsiness, anxiety, peripheral neuropathy, tremor, migraine, impaired memory, vertigo, gynaecomastia, menorrhagia, irregular menstruation, sexual dysfunction, electrolyte disturbances, renal failure, urinary frequency, gout, tinnitus, hearing loss; skin hyperpigmentation; *rarely* intestinal obstruction, gastro-intestinal perforation, inflammatory bowel disease, arrhythmia, atrial fibrillation, myocardial infarction, angina, pulmonary fibrosis, pulmonary hypertension, increased intracranial pressure, convulsions, confusion, haemolytic anaemia, rhabdomyolysis, myopathy, aseptic necrosis of bone, cataract, glaucoma, angioedema, exfoliative dermatitis, and Stevens-Johnson syndrome; *also reported* growth retardation in children

Indications and dose

Chronic phase and advanced phase chronic myeloid leukaemia

- By mouth

Consult local treatment protocol for details

Glivec® (Novartis) (PoM)

Tablets, f/c, imatinib (as mesilate) 100 mg (yellow-brown, scored), net price 60-tab pack = £862.19; 400 mg (yellow), 30-tab pack = £1724.39. Label: 21, 27

Counselling Tablets may be dispersed in water or apple juice

Tretinoin

Tretinoin is licensed for the induction of remission in acute promyelocytic leukaemia. It is used in previously untreated children as well as in those who have relapsed after standard chemotherapy or who are refractory to it.

TRETINOIN

Note Tretinoin is the acid form of vitamin A

Cautions exclude pregnancy before starting treatment, see also Pregnancy below; monitor full blood count and coagulation profile, liver function, serum calcium and plasma lipids before and during treatment; increased risk of thrombo-embolism during first month of treatment; **interactions:** Appendix 1 (retinoids)

Hepatic impairment reduce dose—consult local treatment protocol for details

Renal impairment reduce dose—consult local treatment protocol for details

Pregnancy teratogenic; effective contraception must be used for at least 1 month before oral treatment, during treatment and for at least 1 month after stopping (oral progestogen-only contraceptives **not** considered effective); see also Pregnancy and Reproductive Function, p. 421

Breast-feeding discontinue breast-feeding

Side-effects retinoic acid syndrome (fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, pleural effusion, hyperleukocytosis, hypotension, oedema, weight gain, hepatic, renal and multi-organ failure) requires immediate treatment—consult product literature; gastro-intestinal disturbances, pancreatitis; arrhythmias, flushing, oedema; headache, benign intracranial hypertension (children particularly susceptible—consider dose reduction if intractable headache), shivering, dizziness, confusion, anxiety, depression, insomnia, paraesthesia, visual and hearing disturbances (children particularly susceptible to nervous system effects); raised liver enzymes, serum creatinine and lipids; bone and chest pain, alopecia, erythema, rash, pruritus, sweating, dry skin and mucous membranes, cheilitis; thromboembolism, hypercalcaemia, and genital ulceration reported

Indications and dose

Acute promyelocytic leukaemia

- By mouth

Consult treatment protocol for details

Vesanoid® (Intrapharm) (PoM)

Capsules, yellow/brown, tretinoin 10 mg, net price 100-cap pack = £160.63. Label: 21, 25

8.2 Drugs affecting the immune response

- 8.2.1 Antiproliferative immunosuppressants**
- 8.2.2 Corticosteroids and other immunosuppressants**
- 8.2.3 Anti-lymphocyte monoclonal antibodies**
- 8.2.4 Other immunomodulating drugs**

Immunosuppressant therapy

Immunosuppressants are used to suppress rejection in organ transplant recipients and to treat a variety of chronic inflammatory and autoimmune diseases. Solid organ transplant patients are maintained on drug regimens, which may include antiproliferative drugs (azathioprine or mycophenolate mofetil), calcineurin inhibitors

bitors (ciclosporin or tacrolimus), corticosteroids, or sirolimus. Choice is dependent on the type of organ, time after transplant, and clinical condition of the patient. Specialist management is required and other immunomodulators may be used to initiate treatment or to treat rejection.

Impaired immune responsiveness Infections in the immunocompromised child can be severe and show atypical features. Specific local protocols should be followed for the management of infection. Corticosteroids may suppress clinical signs of infection and allow diseases such as septicaemia or tuberculosis to reach an advanced stage before being recognised. Children should be up-to-date with their childhood vaccinations before initiation of immunosuppressant therapy (e.g. before transplantation); vaccination with varicella-zoster vaccine (section 14.4) is also necessary during this period—**important:** for advice on measles exposure, see section 14.5.1, and chickenpox (varicella) exposure, see section 14.5.2. For advice on the use of live vaccines in individuals with impaired immune response, see section 14.1. For general comments and warnings relating to corticosteroids and immunosuppressants, see section 6.3.2.

Pregnancy Transplant patients immunosuppressed with azathioprine should not discontinue it on becoming pregnant. However, there have been reports of premature birth and low birth-weight following exposure to azathioprine, particularly in combination with corticosteroids. Spontaneous abortion has been reported following maternal or paternal exposure. Azathioprine is teratogenic in *animal* studies.

There is less experience of ciclosporin in pregnancy but it does not appear to be any more harmful than azathioprine. The use of these drugs during pregnancy needs to be supervised in specialist units.

8.2.1 Antiproliferative immunosuppressants

Azathioprine is widely used for transplant recipients and it is also used to treat a number of auto-immune conditions (see section 10.1.3), usually when corticosteroid therapy alone provides inadequate control. It is metabolised to mercaptopurine, and doses should be reduced to one quarter of the original dose when allopurinol is given concurrently. Blood tests and monitoring for signs of myelosuppression are essential in long-term treatment with azathioprine.

Thiopurine methyltransferase

The enzyme thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, tioguanine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Consider measuring TPMT activity before starting azathioprine, mercaptopurine, or tioguanine therapy. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.

Mycophenolate mofetil is metabolised to mycophenolic acid which has a more selective mode of action than azathioprine. It is used in combination with a

corticosteroid and either ciclosporin or tacrolimus for the prophylaxis of acute rejection in transplant recipients. Compared with similar regimens incorporating azathioprine, mycophenolate mofetil may reduce the risk of acute rejection episodes; the risk of opportunistic infections (particularly due to tissue-invasive cytomegalovirus) and the occurrence of blood disorders such as leucopenia may be higher. Children may suffer a high incidence of side-effects, particularly gastrointestinal effects, calling for temporary reduction in dose or interruption of treatment.

Cases of pure red cell aplasia have been reported with azathioprine and with mycophenolate mofetil; dose reduction or discontinuation should be considered under specialist supervision.

NICE guidance (immunosuppressive therapy for renal transplantation in children and adolescents)

See p. 438

Cyclophosphamide (section 8.1.1) is less commonly prescribed as an immunosuppressant.

AZATHIOPRINE

Cautions reduced thiopurine methyltransferase activity (see notes above); monitor for toxicity throughout treatment; monitor full blood count weekly (more frequently with higher doses or if severe hepatic or renal impairment) for first 4 weeks (manufacturer advises weekly monitoring for 8 weeks but evidence of practical value unsatisfactory), thereafter reduce frequency of monitoring to at least every 3 months; **interactions:** Appendix 1 (azathioprine)

Bone marrow suppression Children and their carers should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection

Contra-indications hypersensitivity to mercaptopurine

Hepatic impairment reduce dose; monitor liver function; see also Cautions

Renal impairment reduce dose; see also Cautions

Pregnancy see section 8.2; treatment should not normally be initiated during pregnancy

Breast-feeding present in milk in low concentration; no evidence of harm in small studies—use if potential benefit outweighs risk

Side-effects hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis—calling for immediate withdrawal); dose-related bone marrow suppression (see also Cautions); liver impairment, cholestatic jaundice, hair loss and increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely pancreatitis, pneumonitis, hepatic veno-occlusive disease, lymphoma, red cell aplasia—see notes above

Indications and dose

Suppression of transplant rejection

- By mouth, or (if oral route not possible) by intravenous infusion (see also note below)

Consult local treatment protocol for details

Child 1 month–18 years maintenance, 1–3 mg/kg once daily, adjusted according to response; total daily dose may alternatively be given in 2 divided doses

Severe ulcerative colitis and Crohn's disease section 1.5.3

Systemic lupus erythematosus, vasculitis, autoimmune conditions when corticosteroid therapy alone has proved inadequate section 10.1.3

Administration Consult local treatment protocol for details

For *intravenous injection*, reconstitute 50 mg with 5–15 mL Water for Injections; give over at least 1 minute

For *intravenous infusion*, reconstitute 50 mg with 5–15 mL Water for Injections; dilute requisite dose to a concentration of 0.25–2.5 mg/mL in Glucose 5% or Sodium Chloride 0.9%

Note Intravenous injection is alkaline and very irritant. Intravenous route should therefore be used **only** if oral route not feasible and discontinued as soon as oral route can be tolerated. To reduce irritation flush line with infusion fluid

Azathioprine (Non-proprietary) (PoM)

Tablets, azathioprine 25 mg, net price 28-tab pack = £3.66; 50 mg, 56-tab pack = £3.42. Label: 21

Brands include Azamune®

Imuran® (Aspen) (PoM)

Tablets, both f/c, azathioprine 25 mg (orange), net price 100-tab pack = £10.99; 50 mg (yellow), 100-tab pack = £7.99. Label: 21

Injection, powder for reconstitution, azathioprine (as sodium salt), net price 50-mg vial = £15.38

MYCOPHENOLATE MOFETIL

Cautions monitor full blood count every week for 4 weeks then twice a month for 2 months then every month in the first year (consider interrupting treatment if neutropenia develops); active gastro-intestinal disease (risk of haemorrhage, ulceration and perforation); delayed graft function; increased susceptibility to skin cancer (avoid exposure to strong sunlight); possible decreased effectiveness of vaccination—avoid live vaccines; **interactions:** Appendix 1 (mycophenolate mofetil)

Bone marrow suppression Children and their carers should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding

Renal impairment manufacturer advises consider dose reduction if estimated glomerular filtration rate less than 25 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid—congenital malformations reported; effective contraception required before treatment, during treatment, and for 6 weeks after discontinuation of treatment

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects taste disturbance, gingival hyperplasia, nausea, constipation, flatulence, anorexia, weight loss, diarrhoea, vomiting, abdominal pain, gastro-intestinal inflammation, ulceration, and bleeding, hepatitis, jaundice, pancreatitis, stomatitis, ileus, pleural effusion, oedema, tachycardia, hypertension, hypotension, vasodilatation, cough, dyspnoea, insomnia, agitation, confusion, depression, anxiety, convulsions, paraesthesia, myasthenic syndrome, tremor, dizziness, headache, influenza-like syndrome, infections, hyperglycaemia, renal impairment, malignancy (particularly of the skin), blood disorders (including leucopenia, anaemia, thrombocytopenia, pancytopenia, and red cell aplasia—see notes above),

disturbances of electrolytes and blood lipids, arthralgia, alopecia, acne, skin hypertrophy, and rash; *also reported* intestinal villous atrophy, progressive multifocal leucoencephalopathy, interstitial lung disease, pulmonary fibrosis

Licensed use not licensed for use in children under 2 years for the prophylaxis of acute rejection in renal transplantation; not licensed for use in children for the prophylaxis of acute rejection in hepatic transplantation

Indications and dose

Prophylaxis of acute rejection in renal transplantation in combination with a corticosteroid and ciclosporin

• By mouth

Consult local treatment protocol for details

Child 1 month–18 years 600 mg/m² twice daily (max. 2 g daily)

Prophylaxis of acute rejection in renal transplantation in combination with a corticosteroid and tacrolimus

• By mouth

Consult local treatment protocol for details

Child 1 month–18 years 300 mg/m² twice daily (max. 2 g daily)

Prophylaxis of acute rejection in hepatic transplantation in combination with a corticosteroid and ciclosporin or tacrolimus

• By mouth

Consult local treatment protocol for details

Child 1 month–18 years 10 mg/kg twice daily, increased to 20 mg/kg twice daily (max. 2 g daily)

Note Tablets and capsules not appropriate for dose titration in children with body surface area less than 1.25 m²

Mycophenolate Mofetil (Non-proprietary) (PoM)

Capsules, mycophenolate mofetil 250 mg, net price 100-cap pack = £82.26

Tablets, mycophenolate mofetil 500 mg, net price 50-tab pack = £11.82

Brands include Arzip®

CellCept® (Roche) (PoM)

Capsules, blue/brown, mycophenolate mofetil 250 mg, net price 100-cap pack = £82.26

Tablets, lavender, mycophenolate mofetil 500 mg, net price 50-tab pack = £82.26

Oral suspension, mycophenolate mofetil 1 g/5 mL when reconstituted with water, net price 175 mL = £115.16

Excipients include aspartame (section 9.4.1)

8.2.2 Corticosteroids and other immunosuppressants

The corticosteroids prednisolone and dexamethasone are widely used in paediatric oncology; they have a marked antitumour effect. Dexamethasone is preferred for acute lymphoblastic leukaemia whilst prednisolone may be used for Hodgkin's disease, non-Hodgkin's lymphoma, and B-cell lymphoma and leukaemia.

Dexamethasone is the corticosteroid of choice in paediatric supportive and palliative care. For children who are not receiving a corticosteroid as a component of

their chemotherapy, dexamethasone may be used to reduce raised intracranial pressure (see p. 19), or to help control emesis when combined with an appropriate anti-emetic (see p. 18). For more information on glucocorticoid therapy, including the disadvantages of treatment, see section 6.3.2.

The corticosteroids are also powerful immunosuppressants. They are used to prevent organ transplant rejection, and in high dose to treat rejection episodes.

Ciclosporin (cyclosporin), a calcineurin inhibitor, is a potent immunosuppressant which is virtually non-myelotoxic but markedly nephrotoxic. It may be used in organ and tissue transplantation, for prevention of graft rejection following bone marrow, kidney, liver, pancreas, heart, lung, and heart-lung transplantation, and for prophylaxis and treatment of graft-versus-host disease. Ciclosporin also has a role in steroid-sensitive and steroid-resistant nephrotic syndrome; in corticosteroid-sensitive nephrotic syndrome it may be given with prednisolone (section 6.3).

Tacrolimus is also a calcineurin inhibitor. Although not chemically related to ciclosporin it has a similar mode of action and side-effects.

Sirolimus is a non-calcineurin inhibiting immunosuppressant.

Basiliximab is a monoclonal antibody that prevents T-lymphocyte proliferation; it is used for prophylaxis of acute rejection in allogeneic renal transplantation. It is given with ciclosporin and corticosteroid immunosuppression regimens; its use should be confined to specialist centres.

Antithymocyte immunoglobulin (rabbit) is used for the prophylaxis of organ rejection in renal and heart allograft recipients and for the treatment of corticosteroid-resistant allograft rejection in renal transplantation. Tolerability is increased by pretreatment with an intravenous corticosteroid and antihistamine; an antipyretic drug such as paracetamol may also be beneficial.

NICE guidance

Immunosuppressive therapy for renal transplantation in children and adolescents (April 2006)

NICE has recommended that for induction therapy in the prophylaxis of organ rejection, either basiliximab or daclizumab [discontinued] are options for combining with a calcineurin inhibitor. For each individual, ciclosporin or tacrolimus is chosen as the calcineurin inhibitor on the basis of side-effects. Mycophenolate mofetil is recommended as part of an immunosuppressive regimen **only if**:

- the calcineurin inhibitor is not tolerated, particularly if nephrotoxicity endangers the transplanted kidney; or
- there is very high risk of nephrotoxicity from the calcineurin inhibitor, requiring a reduction in the dose of the calcineurin inhibitor or its avoidance.

Mycophenolic acid is not recommended as part of an immunosuppressive regimen for renal transplantation in children or adolescents.

Sirolimus [not licensed for use in children] is recommended as a component of immunosuppressive regimen **only if** intolerance necessitates the withdrawal of a calcineurin inhibitor.

These recommendations may not be consistent with the marketing authorisation of some of the products.

www.nice.org.uk/TA99

ANTITHYMOCYTE IMMUNOGLOBULIN (RABBIT)

Cautions see notes above; monitor blood count

Contra-indications infection

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, dysphagia, diarrhoea; hypotension; infusion-related reactions (including cytokine release syndrome and anaphylaxis, see notes above), serum sickness; fever, shivering, increased susceptibility to infection; increased susceptibility to malignancy; lymphopenia, neutropenia, thrombocytopenia; myalgia; pruritus, rash

Indications and dose

Heart transplantation

- By intravenous infusion over at least 6 hours

Child 1 month–18 years 1–2.5 mg/kg daily for 3–5 days starting the day of transplantation

Note To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight

Renal transplantation

- By intravenous infusion over at least 6 hours

Child 1–18 years 1–1.5 mg/kg daily for 3–9 days starting the day of transplantation

Note To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight

Corticosteroid-resistant renal graft rejection

- By intravenous infusion over at least 6 hours

Child 1–18 years 1.5 mg/kg daily for 7–14 days

Note To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight

Administration For *continuous intravenous infusion* reconstitute each vial with 5 mL water for injections to produce a solution of 5 mg/mL; gently rotate to dissolve. Dilute requisite dose with Glucose 5% or Sodium Chloride 0.9% to an approx. concentration of 0.5 mg/mL; begin infusion immediately after dilution; give through an in-line filter (pore size 0.22 micron); incompatible with unfractionated heparin and hydrocortisone in glucose infusion—precipitation reported

Thymoglobuline® (Sanofi Aventis) **[PoM]**

Intravenous infusion, powder for reconstitution, rabbit anti-human thymocyte immunoglobulin, net price 25-mg vial = £158.77

BASILIXIMAB

Pregnancy manufacturer advises avoid—no information available; adequate contraception must be used during treatment and for 16 weeks after last dose

Breast-feeding manufacturer advises avoid—no information available

Side-effects severe hypersensitivity reactions and cytokine release syndrome reported

Indications and dose

Prophylaxis of acute rejection in allogeneic renal transplantation used in combination with ciclosporin and corticosteroid-containing immunosuppression regimens

- By intravenous injection or by intravenous infusion

Consult local treatment protocol for details

Child over 1 year, body-weight under 35 kg 10 mg within 2 hours before transplant surgery and 10 mg 4 days after surgery

Child body-weight over 35 kg 20 mg within 2 hours before transplant surgery and 20 mg 4 days after surgery

Note Withhold second dose if severe hypersensitivity or graft loss occurs

Administration For intravenous infusion, dilute reconstituted solution to a concentration not exceeding 400 micrograms/mL, with Glucose 5% or Sodium Chloride 0.9%; give over 20–30 minutes

Simulect® (Novartis) (PoM)

Injection, powder for reconstitution, basiliximab, net price 10-mg vial = £758.69, 20-mg vial = £842.38 (both with water for injections). For intravenous infusion

CYCLOSPORIN

(Cyclosporin)

Cautions monitor kidney function—dose dependent increase in serum creatinine and urea during first few weeks may necessitate discontinuation (exclude rejection of kidney transplant); monitor liver function (see also Hepatic Impairment below); monitor blood pressure—discontinue if hypertension develops that cannot be controlled by antihypertensives; hyperuricaemia; monitor serum potassium especially in renal dysfunction (risk of hyperkalaemia); monitor serum magnesium; measure blood lipids before treatment and after the first month of treatment; monitor whole blood ciclosporin concentration (trough level dependent on indication—consult local treatment protocol for details); use with tacrolimus specifically contra-indicated; for patients other than transplant recipients, preferably avoid other immunosuppressants (increased risk of infection and malignancies, including lymphoma and skin cancer); avoid excessive exposure to UV light, including sunlight; **interactions:** Appendix 1 (ciclosporin)

Additional cautions in nephrotic syndrome *Contra-indicated* in uncontrolled hypertension, uncontrolled infections, and malignancy; in long-term management, perform renal biopsies every 1–2 years

Additional cautions Atopic Dermatitis and Psoriasis, section 13.5.3; Rheumatoid Arthritis, section 10.1.3

Hepatic impairment dosage adjustment based on bilirubin and liver enzymes may be needed

Renal impairment dose as in normal renal function but see Cautions above; in *nephrotic syndrome* reduce dose by 25–50% if serum creatinine more than 30% above baseline on more than one measurement

Pregnancy crosses placenta; see Immunosuppressant Therapy, p. 436

Breast-feeding present in milk—manufacturer advises avoid

Side-effects anorexia, nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia, hepatic dysfunction, hypertension, tremor, headache, paraes-

thesia, fatigue, renal dysfunction (renal structural changes on long-term administration; see also under Cautions), hyperuricaemia, hyperkalaemia, hypomagnesaemia, hyperlipidaemia, hypercholesterolaemia, muscle cramps, myalgia, hypertrichosis; *less commonly* oedema, weight gain, signs of encephalopathy, anaemia, thrombocytopenia; *rarely* pancreatitis, motor polyneuropathy, menstrual disturbances, gynaecomastia, micro-angiopathic haemolytic anaemia, haemolytic uraemic syndrome, hyperglycaemia, muscle weakness, myopathy, visual disturbances secondary to benign intracranial hypertension (discontinue); *also reported with infusion* anaphylaxis

Licensed use not licensed for use in children under 3 months

Indications and dose

Prevention of graft rejection following bone-marrow, kidney, liver, pancreas, heart, lung, and heart-lung transplantation, prophylaxis and treatment of graft-versus-host disease

- By mouth or by intravenous infusion

Consult local treatment protocols for details

Nephrotic syndrome see also section 6.3.2, p. 377

- By mouth

Child 1 month–18 years 3 mg/kg twice daily, increase if necessary in corticosteroid-resistant disease; for maintenance reduce to lowest effective dose according to whole blood-ciclosporin concentrations, proteinuria, and renal function

Refractory ulcerative colitis section 1.5.3

Severe psoriasis, severe eczema section 13.5.3

Important

Patients should be stabilised on a particular brand of oral ciclosporin because switching between formulations without close monitoring may lead to clinically important changes in blood-ciclosporin concentration. Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching. If it is necessary to switch a patient to a different brand of ciclosporin, the patient should be monitored closely for changes in blood-ciclosporin concentration, serum-creatinine, blood pressure, and transplant function.

Capimune® (Mylan) (PoM)

Capsules, ciclosporin 25 mg (grey), net price 30-cap pack = £13.50; 50 mg (white), 30-cap pack = £26.80; 100 mg (grey), 30-cap pack = £51.30. Counselling, administration

Excipients include propylene glycol (see Excipients, p. 2)

Note Contains ethanol

Counselling Total daily dose should be taken in 2 divided doses

Capsorin® (Morningside) (PoM)

Capsules, ciclosporin 25 mg (grey), net price 30-cap pack = £13.11; 50 mg (white), 30-cap pack = £25.65; 100 mg (grey), 30-cap pack = £48.93. Counselling, administration

Note Contains ethanol

Counselling Total daily dose should be taken in 2 divided doses

Dexamime® (Dexcel) (PoM)

Capsules, grey, ciclosporin 25 mg, net price 30-cap pack = £13.06; 50 mg 30-cap pack = £25.60; 100 mg 30-cap pack = £48.90. Counselling, administration

Note Contains ethyl lactate which is metabolised to ethanol
Counselling Total daily dose should be taken in 2 divided doses

Neoral® (Novartis) (PoM)

Capsules, ciclosporin 10 mg (yellow/white), net price 60-cap pack = £19.40; 25 mg (blue/grey), 30-cap pack = £19.52; 50 mg (yellow/white), 30-cap pack = £38.23; 100 mg (blue/grey), 30-cap pack = £72.57. Counselling, administration

Excipients include propylene glycol (see Excipients, p. 2)
Note Contains ethanol

Oral solution, yellow, sugar-free, ciclosporin 100 mg/mL, net price 50 mL = £108.73. Counselling, administration

Excipients include propylene glycol (see Excipients, p. 2)
Note Contains ethanol

Counselling Total daily dose should be taken in 2 divided doses

Mix solution with orange juice (or squash) or apple juice (to improve taste) or with water immediately before taking (and rinse with more to ensure total dose). Do not mix with grapefruit juice. Keep medicine measure away from other liquids (including water)

Sandimmun® (Novartis) (PoM)

Concentrate for intravenous infusion (oily), ciclosporin 50 mg/mL. To be diluted before use, net price 1-mL amp = £1.94; 5-mL amp = £9.17

Excipients include polyoxyl castor oil (risk of anaphylaxis, see Excipients, p. 2)

Note Contains ethanol

Administration For *intravenous infusion*, dilute to a concentration of 0.5–2.5 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 2–6 hours; not to be used with PVC equipment; observe patient for signs of anaphylaxis for at least 30 minutes after starting infusion and at frequent intervals thereafter
Note Capsules and oral solution available direct from Novartis for children who cannot be transferred to a different oral preparation

SIROLIMUS

Cautions monitor renal function when given with ciclosporin; monitor whole blood-sirolimus trough concentration (Afro-Caribbean patients may require higher doses); hyperlipidaemia (monitor lipids); monitor urine proteins; increased susceptibility to infection (especially urinary-tract infection); increased susceptibility to lymphoma and other malignancies, particularly of the skin (limit exposure to UV light); **interactions:** Appendix 1 (sirolimus)

Hepatic impairment monitor blood-sirolimus trough concentration; dose reduction may be necessary, consult local treatment protocol for details

Pregnancy avoid unless essential—toxicity in *animal* studies; effective contraception must be used during treatment and for 12 weeks after stopping

Breast-feeding discontinue breast-feeding

Side-effects abdominal pain, constipation, nausea, diarrhoea, ascites, stomatitis, oedema, tachycardia, hypertension, hypercholesterolaemia, hypertriglyceridaemia, venous thromboembolism, pleural effusion, pneumonitis, headache, pyrexia, proteinuria, haemolytic uraemic syndrome, anaemia, thrombocytopenia, thrombotic thrombocytopenic purpura, leucopenia, neutropenia, hypokalaemia, hypophosphataemia,

hyperglycaemia, lymphocele, arthralgia, osteonecrosis, epistaxis, acne, rash, impaired healing; *less commonly* pancreatitis, pulmonary embolism, pulmonary haemorrhage, pericardial effusion, nephrotic syndrome, pancytopenia; *rarely* interstitial lung disease, alveolar proteinosis, hepatic necrosis, lymphoedema, hypersensitivity reactions (including anaphylactic reactions, angiodema, exfoliative dermatitis, hypersensitivity vasculitis); *also reported* focal segmental glomerulosclerosis, reversible impairment of male fertility

Licensed use not licensed for use in children

Indications and dose

See NICE guidance, p. 438

- By mouth

Consult local treatment protocols for details

Rapamune® (Pfizer) (PoM)

Tablets, coated, sirolimus 0.5 mg (tan), net price 30-tab pack = £69.00; 1 mg (white), 30-tab pack = £86.49; 2 mg (yellow), 30-tab pack = £172.98. Counselling, administration

Important The 0.5-mg tablet is not bioequivalent to the 1-mg, 2-mg, and 5-mg tablets. Multiples of 0.5-mg tablets should not be used as a substitute for other tablet strengths

Oral solution, sirolimus 1 mg/mL, net price 60 mL = £162.41. Counselling, administration

Note Contains ethanol

Administration food may affect absorption (give at the same time with respect to food). Mix solution with at least 60 mL water or orange juice in a glass or plastic container immediately before taking; refill container with at least 120 mL of water or orange juice and drink immediately (to ensure total dose). Do not mix with any other liquids

TACROLIMUS

Cautions monitor blood pressure, ECG (**important:** see cardiomyopathy below), fasting blood-glucose concentration, haematological and neurological (including visual) parameters, electrolytes, hepatic and renal function; monitor whole blood-tacrolimus trough concentration (especially during episodes of diarrhoea)—consult local treatment protocol for details; QT-interval prolongation; neurotoxicity; increased risk of infections, malignancies, and lymphoproliferative disorders; avoid excessive exposure to UV light (including sunlight); **interactions:** Appendix 1 (tacrolimus)

Skilled tasks May affect performance of skilled tasks (e.g. driving)

Contra-indications hypersensitivity to macrolides; avoid concurrent administration with ciclosporin (care if patient has previously received ciclosporin)

Hepatic impairment dose reduction may be necessary in severe impairment

Pregnancy exclude before treatment; avoid unless potential benefit outweighs risk—risk of premature delivery, intra-uterine growth restriction, and hyperkalaemia

Breast-feeding avoid—present in breast milk

Side-effects nausea, vomiting, diarrhoea, constipation, dyspepsia, flatulence, bloating, weight changes, anorexia, gastro-intestinal inflammation, ulceration, and perforation, hepatic dysfunction, jaundice, cholestasis, ascites, bile-duct abnormalities, oedema, tachycardia, hypertension, haemorrhage, thromboembolic and ischaemic events, dyspnoea, pleural

effusion, parenchymal lung disorders, sleep disturbances, tremor, headache, peripheral neuropathy, mood changes, depression, confusion, anxiety, psychosis, seizures, paraesthesia, dizziness, renal impairment, renal failure, renal tubular necrosis, urinary abnormalities, hyperglycaemia, electrolyte disturbances (including hyperkalaemia, hypokalaemia, and hyperuricaemia), blood disorders (including anaemia, leucopenia, pancytopenia, and thrombocytopenia), arthralgia, muscle cramp, visual disturbances, photophobia, tinnitus, impaired hearing, alopecia, sweating, acne; *less commonly* paralytic ileus, gastro-intestinal reflux disease, peritonitis, pancreatitis, heart failure, arrhythmia, cardiac arrest, cerebrovascular accident, cardiomyopathy (**important**: see Cardiomyopathy below), palpitation, respiratory failure, coma, speech disorder, amnesia, paralysis, influenza-like symptoms, encephalopathy, coagulation disorders, cataract, photosensitivity, hypoglycaemia, dysmenorrhoea, hypertension, dermatitis; *rarely* pericardial effusion, respiratory distress syndrome, posterior reversible encephalopathy syndrome, dehydration, thrombotic thrombocytopenic purpura, blindness, toxic epidermal necrolysis, hirsutism; *very rarely* myasthenia, haemorrhagic cystitis, Stevens Johnson syndrome; *also reported* pure red cell aplasia, agranulocytosis, haemolytic anaemia

Cardiomyopathy Cardiomyopathy has been reported in children. Children should be monitored by echocardiography for hypertrophic changes—consider dose reduction or discontinuation if these occur

Licensed use *Advagraf*® not licensed for use in children

Indications and dose

See under preparations and consult local treatment protocols

Atopic eczema (topical use) section 13.5.3

MHRA/CHM advice

Oral tacrolimus products: prescribe and dispense by brand name only, to minimise the risk of inadvertent switching between products, which has been associated with reports of toxicity and graft rejection (June 2012)

Inadvertent switching between oral tacrolimus products has been associated with reports of toxicity and graft rejection. To ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only.

- *Adoport*®, *Prograf*®, *Capexion*®, *Tacni*®, and *Vivadex*® are immediate-release capsules taken twice daily, once in the morning and once in the evening;
- *Modigraf*® granules are used to prepare an immediate-release oral suspension which is taken twice daily, once in the morning and once in the evening;
- *Advagraf*® is a prolonged-release capsule that is taken once daily in the morning.

Switching between tacrolimus brands requires careful supervision and therapeutic monitoring by an appropriate specialist.

Administration For *continuous intravenous infusion* over 24 hours, dilute to a concentration of 4–100 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%, to a total volume between 20–500 mL. Tacrolimus is incompatible with PVC

Adoport® (Sandoz) (PoM)

Capsules, tacrolimus (as monohydrate) 500 micrograms (white/ivory), net price 50-cap pack = £42.92; 1 mg (white/brown), 50-cap pack = £55.69, 100-cap pack = £111.36; 5 mg (white/orange), 50-cap pack = £205.74. Label: 23, counselling, skilled tasks

Dose

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation

• By mouth

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

• By mouth

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Note A lower initial dose of 100 micrograms/kg twice daily has been used in adolescents to prevent very high 'trough' concentrations

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

• By mouth

Neonate initially 150 micrograms/kg twice daily as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

• By mouth

Neonate initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Allograft rejection resistant to conventional immunosuppressive therapy Consult local treatment protocol

Capexion® (Generics) (PoM)

Capsules, tacrolimus 500 micrograms, (ivory), net price 50-cap pack = £52.50; 1 mg (white), 50-cap pack = £68.20, 100-cap pack = £136.20; 5 mg (red), 50-cap pack = £252.00. Label: 23, counselling, skilled tasks

Dose

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation

• By mouth

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

● By mouth

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Note A lower initial dose of 100 micrograms/kg twice daily has been used in adolescents to prevent very high 'trough' concentrations

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

● By mouth

Neonate initially 150 micrograms/kg twice daily, as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

● By mouth

Neonate initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Allograft rejection resistant to conventional immunosuppressive therapy Consult local treatment protocol**Modigraf®** (Astellas) ▼ (PoM)

Granules, tacrolimus (as monohydrate), 200 micrograms, net price 50-sachet pack = £71.30; 1 mg, 50-sachet pack = £356.65. Label: 13, 23, counselling, skilled tasks

Dose**Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation**

● By mouth

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

● By mouth

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Note A lower initial dose of 100 micrograms/kg twice daily has been used in adolescents to prevent very high 'trough' concentrations

Prophylaxis of graft rejection following heart transplantation without antibody induction starting within 12 hours of transplantation

● By mouth

Neonate initially 150 micrograms/kg twice daily as soon as clinically possible (8–12 hours after discontinuing intravenous infusion), adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily as soon as clinically possible (8–12 hours after discontinuing intravenous infusion), adjusted according to whole-blood concentration

Prophylaxis of graft rejection following heart transplantation following antibody induction starting within 5 days of transplantation

● By mouth

Neonate initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Allograft rejection resistant to conventional immunosuppressive therapy Consult local treatment protocol

Note The *Scottish Medicines Consortium* (p. 3) has advised (November 2010) that tacrolimus granules for oral suspension (*Modigraf®*) are accepted for restricted use within NHS Scotland in patients for whom tacrolimus is an appropriate choice of immunosuppressive therapy and where small changes (less than 500 micrograms) in dosing increments are required (such as, in paediatric patients) or in seriously ill patients who are unable to swallow tacrolimus capsules.

Prograf® (Astellas) (PoM)

Capsules, tacrolimus (as monohydrate) 500 micrograms (yellow), net price 50-cap pack = £61.88; 1 mg (white), 50-cap pack = £80.28, 100-cap pack = £160.54; 5 mg (greyish-red), 50-cap pack = £296.58. Label: 23, counselling, skilled tasks

Concentrate for intravenous infusion, tacrolimus 5 mg/mL. To be diluted before use. Net price 1-mL amp = £58.45

Excipients include polyoxyl castor oil (risk of anaphylaxis, see Excipients, p. 2)

Dose**Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation**

● By mouth

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

● By continuous intravenous infusion (only if oral route inappropriate)

Neonate 50 micrograms/kg over 24 hours for up to 7 days (then transfer to oral therapy), adjusted according to whole-blood concentration

Child 1 month–18 years 50 micrograms/kg over 24 hours for up to 7 days (then transfer to oral therapy), adjusted according to whole-blood concentration

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

● By mouth

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Note A lower initial dose of 100 micrograms/kg twice daily has been used in adolescents to prevent very high 'trough' concentrations

● By continuous intravenous infusion (only if oral route inappropriate)

Neonate 75–100 micrograms/kg over 24 hours for up to 7 days (then transfer to oral therapy), adjusted according to whole-blood concentration

Child 1 month–18 years 75–100 micrograms/kg over 24 hours for up to 7 days (then transfer to oral therapy), adjusted according to whole-blood concentration

Prophylaxis of graft rejection following heart transplantation *without antibody induction*, starting within 12 hours of transplantation

- **By mouth**

Neonate initially 150 micrograms/kg twice daily as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

- **By continuous intravenous infusion**

Neonate 30–50 micrograms/kg over 24 hours for up to 7 days (then transfer to oral therapy), adjusted according to whole-blood concentration

Child 1 month–18 years 30–50 micrograms/kg over 24 hours for up to 7 days (then transfer to oral therapy), adjusted according to whole-blood concentration

Prophylaxis of graft rejection following heart transplantation *following antibody induction*, starting within 5 days of transplantation

- **By mouth**

Neonate initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Allograft rejection resistant to conventional immunosuppressive therapy Consult local treatment protocol

Tacni[®] (TEVA UK) (PoM)

Capsules, tacrolimus 500 micrograms (ivory), net price 50-cap pack = £50.48; 1 mg (white), 50-cap pack = £65.49, 100-cap pack = £130.99; 5 mg (red), 50-cap pack = £242.01. Label: 23, counselling, skilled tasks

Dose

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation

- **By mouth**

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

- **By mouth**

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Note A lower initial dose of 100 micrograms/kg twice daily has been used in adolescents to prevent very high 'trough' concentrations

Prophylaxis of graft rejection following heart transplantation *without antibody induction*, starting within 12 hours of transplantation

- **By mouth**

Neonate initially 150 micrograms/kg twice daily, as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

Prophylaxis of graft rejection following heart transplantation *following antibody induction*, starting within 5 days of transplantation

- **By mouth**

Neonate initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Allograft rejection resistant to conventional immunosuppressive therapy Consult local treatment protocol

Vivadex[®] (Dexcel) (PoM)

Capsules, tacrolimus 500 micrograms (ivory), net price 50-cap pack = £46.41; 1 mg (white), 50-cap pack = £60.21, 100-cap pack = £120.41; 5 mg (red), 50-cap pack = £222.44. Label: 23, counselling, skilled tasks

Dose

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation

- **By mouth**

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

- **By mouth**

Neonate initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Note A lower initial dose of 100 micrograms/kg twice daily has been used in adolescents to prevent very high 'trough' concentrations

Prophylaxis of graft rejection following heart transplantation *without antibody induction*, starting within 12 hours of transplantation

- **By mouth**

Neonate initially 150 micrograms/kg twice daily as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

Child 1 month–18 years initially 150 micrograms/kg twice daily as soon as clinically possible (8–12 hours after discontinuation of intravenous infusion), adjusted according to whole-blood concentration

Prophylaxis of graft rejection following heart transplantation *following antibody induction*, starting within 5 days of transplantation

- **By mouth**

Neonate initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Child 1 month–18 years initially 50–150 micrograms/kg twice daily, adjusted according to whole-blood concentration

Allograft rejection resistant to conventional immunosuppressive therapy Consult local treatment protocol

■ **Modified release**

Advagraf[®] is not licensed for use in children

Advagraf[®] (Astellas) (PoM)

Capsules, m/r, tacrolimus (as monohydrate) 500 micrograms (yellow/orange), net price 50-cap pack = £35.79; 1 mg (white/orange), 50-cap pack =

£71.59, 100-cap pack = £143.17; 3 mg (red/orange), 50-cap pack = £214.76; 5 mg (red/orange), 50-cap pack = £266.92. Label: 23, 25, counselling, skilled tasks

8.2.3 Anti-lymphocyte monoclonal antibodies

Rituximab, a monoclonal antibody which causes lysis of B lymphocytes, has been used as a component of the treatment of post-transplantation lymphoproliferative disease, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and severe cases of resistant immune modulated disease including idiopathic thrombocytopenia purpura, haemolytic anaemia, and systemic lupus erythematosus. Full resuscitation facilities should be at hand and as with other cytotoxics, treatment should be undertaken under the close supervision of a specialist.

Rituximab should be used with caution in children receiving cardiotoxic chemotherapy or with a history of cardiovascular disease; in adults exacerbation of angina, arrhythmia, and heart failure have been reported. Transient hypotension occurs frequently during infusion and antihypertensives may need to be withheld for 12 hours before infusion. Progressive multifocal leucoencephalopathy (which is usually fatal or causes severe disability) has been reported in association with rituximab; children treated with rituximab should be monitored for cognitive, neurological, or psychiatric signs and symptoms. If progressive multifocal leucoencephalopathy is suspected, suspend treatment until it has been excluded. Severe (including fatal) skin reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported—permanently discontinue treatment if severe skin reactions occur.

Infusion-related side-effects (including cytokine release syndrome) are reported commonly with rituximab and occur predominantly during the first infusion; they include fever and chills, nausea and vomiting, allergic reactions (such as rash, pruritus, angioedema, bronchospasm and dyspnoea), flushing and tumour pain. Children should be given paracetamol and an antihistamine before each dose of rituximab to reduce these effects. Premedication with a corticosteroid should also be considered. The infusion may have to be stopped temporarily and the infusion-related effects treated—consult product literature or local treatment protocol for appropriate management. Evidence of pulmonary infiltration and features of tumour lysis syndrome should be sought if infusion-related effects occur.

Fatalities following severe cytokine release syndrome (characterised by severe dyspnoea) and associated with features of tumour lysis syndrome have occurred 1–2 hours after infusion of rituximab. Children with a high tumour burden as well as those with pulmonary insufficiency or infiltration are at increased risk and should be monitored **very closely** (and a slower rate of infusion considered).

Hepatitis B infection and reactivation (including fatal cases) has been reported in patients taking rituximab. All children should be screened before treatment. Children with positive hepatitis B serology should be

referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; treatment should not be initiated in children with active hepatitis B infection. Children should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for several months following the last infusion (consult product literature).

Alemtuzumab is no longer licensed but is available through a patient access programme for oncological and transplant indications.

RITUXIMAB

Cautions see notes above—but for full details (including monitoring) consult product literature or local treatment protocol

Pregnancy avoid unless potential benefit to mother outweighs risk of B-lymphocyte depletion in fetus—effective contraception (in both sexes) required during and for 12 months after treatment

Breast-feeding avoid breast-feeding during and for 12 months after treatment

Side-effects see notes above—but for full details (including monitoring and management of side-effects) consult product literature

Licensed use not licensed for use in children

Indications and dose

See notes above

• By intravenous infusion

Consult local treatment protocol for details

MabThera® (Roche) (PoM)

Concentrate for intravenous infusion, rituximab

10 mg/mL, net price 10-mL vial = £174.63, 50-mL vial = £873.15

8.2.4 Other immunomodulating drugs

Interferon alfa

Interferon alfa has shown some antitumour effect and may have a role in inducing early regression of life-threatening corticosteroid-resistant haemangiomas of infancy. Interferon alfa preparations are also used in the treatment of chronic hepatitis B, and chronic hepatitis C ideally in combination with ribavirin (section 5.3.3). Interferon alfa should always be used under the close supervision of a specialist; the decision to treat should be made only after careful assessment of the expected benefits versus the potential risks, in particular the risk of growth inhibition caused by combination therapy. Side-effects are dose-related, but commonly include anorexia, nausea, influenza-like symptoms, and lethargy. Ocular side-effects and depression (including suicidal behaviour) have also been reported—treatment should not be initiated in children with a history of severe psychiatric illness. Myelosuppression may occur, particularly affecting granulocyte counts. Cardiovascular problems (hypotension, hypertension, and arrhythmias), nephrotoxicity and hepatotoxicity have been reported and monitoring of hepatic function is recommended. Hypertriglyceridaemia, sometimes severe, has been observed; monitoring of lipid concen-

tration is recommended. Other side-effects include hypersensitivity reactions, thyroid abnormalities, hyperglycaemia, alopecia, psoriasisiform rash, confusion, coma and seizures, and reversible motor problems in young children. Rarely pulmonary infiltrates, pneumonitis, and pneumonia have occurred; respiratory symptoms should be investigated and if pulmonary infiltrates are suspected or lung function is impaired the discontinuation of interferon alfa should be considered.

Polyethylene glycol-conjugated ('pegylated') derivatives of interferon alfa (**peginterferon alfa-2a** and **peginterferon alfa-2b**) are available; pegylation increases the persistence of the interferon in the blood. The peginterferons are licensed in combination with ribavirin (see section 5.3.3) for the treatment of chronic hepatitis C in previously untreated children and adolescents without liver decompensation.

INTERFERON ALFA

Cautions consult product literature and local treatment protocol for details; **interactions:** Appendix 1 (interferons)

Contra-indications consult product literature and local treatment protocol for details; avoid injections containing benzyl alcohol in neonates (see under preparations below)

Hepatic impairment close monitoring in mild to moderate impairment; avoid if severe

Renal impairment close monitoring required in mild to moderate impairment; avoid in severe impairment

Pregnancy avoid unless potential benefit outweighs risk (toxicity in *animal* studies); effective contraception required during treatment—consult product literature

Breast-feeding unlikely to be harmful

Side-effects see notes above, consult product literature and local treatment protocols for details

Licensed use not licensed for use in children for chronic active hepatitis B; *Roferon-A*® not licensed for use in children

Indications and dose

Induction of early regression of life-threatening corticosteroid resistant haemangiomas of infancy

- By subcutaneous injection

Consult local treatment protocol for details

Chronic active hepatitis B infection see under preparations below

Chronic active hepatitis C infection see under preparations below

IntronA® (MSD) (PoM)

Injection, interferon alfa-2b (rbe) 10 million units/mL, net price 1-mL vial = £41.55, 2.5-mL vial = £103.94. For subcutaneous injection or intravenous infusion

Injection pen, interferon alfa-2b (rbe), net price 15 million units/mL, 1.5-mL cartridge = £74.83; 25 million units/mL, 1.5-mL cartridge = £124.72; 50 million units/mL, 1.5-mL cartridge = £249.45. For subcutaneous injection

Note Each 1.5-mL multidose cartridge delivers 6 doses of 0.2 mL i.e. a total of 1.2 mL

Dose

Chronic active hepatitis B

- By subcutaneous injection

Child 2–18 years 5–10 million units/m² 3 times weekly

Chronic active hepatitis C (in combination with oral ribavirin, see p. 333)

- By subcutaneous injection

Child 3–18 years 3 million units/m² 3 times weekly

Roferon-A® (Roche) (PoM)

Injection, interferon alfa-2a (rbe). Net price 6 million units/mL, 0.5-mL (3 million-unit) prefilled syringe = £14.20; 9 million units/mL, 0.5-mL (4.5 million-unit) prefilled syringe = £21.29; 12 million units/mL, 0.5-mL (6 million-unit) prefilled syringe = £28.37; 18 million units/mL, 0.5-mL (9 million-unit) prefilled syringe = £42.57. For subcutaneous injection

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Dose

Chronic active hepatitis B

- By subcutaneous injection

Child 2–18 years 2.5–5 million units/m² 3 times weekly; up to 10 million units/m² has been used 3 times weekly

PEGINTERFERON ALFA

Cautions consult product literature; **interactions:** Appendix 1 (interferons)

Contra-indications consult product literature

Hepatic impairment avoid in severe impairment

Renal impairment close monitoring required—reduce dose in moderate to severe impairment; consult product literature

Pregnancy manufacturers recommend avoid unless potential benefit outweighs risk (toxicity in *animal* studies); effective contraception required during treatment—consult product literature

Breast-feeding manufacturers advise avoid—no information available

Side-effects see notes above and consult product literature

Indications and dose

Chronic hepatitis C infection (in combination with ribavirin) in previously untreated children without liver decompensation see under preparations below

Pegasy® (Roche) (PoM)

Injection, peginterferon alfa-2a (rbe), net price 90-microgram prefilled syringe £76.51, 135-microgram prefilled syringe = £107.76, 180-microgram prefilled syringe = £124.40; 135-microgram prefilled pen = £107.76, 180-microgram prefilled pen = £124.40. For subcutaneous injection

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Dose

Chronic hepatitis C (in combination with ribavirin) in previously untreated children without liver decompensation

- By subcutaneous injection

Child 5–18 years consult product literature

ViraferonPeg® (MSD) (PoM)

Injection, prefilled pen, powder for reconstitution, peginterferon alfa-2b (rbe), net price 50-microgram pen = £66.46, 80-microgram pen = £106.34, 100-microgram pen = £132.92, 120-microgram pen = £159.51, 150-microgram pen = £199.38 (all with needles and swabs). For subcutaneous injection

Dose

Chronic hepatitis C (in combination with ribavirin in previously untreated children without liver decompensation)

- By subcutaneous injection

Child 3–18 years consult product literature

Interferon gamma

Interferon gamma-1b is used to reduce the frequency of serious infection in chronic granulomatous disease and in severe malignant osteopetrosis.

INTERFERON GAMMA-1b
(Immune interferon)

Cautions seizure disorders (including seizures associated with fever); cardiac disease (including ischaemia, congestive heart failure, and arrhythmias); monitor before and during treatment: haematological tests (including full blood count, differential white cell count, and platelet count), blood chemistry tests (including renal and liver function tests) and urinalysis; avoid simultaneous administration of foreign proteins including immunological products (risk of exaggerated immune response); **interactions:** Appendix 1 (interferons)

Hepatic impairment manufacturer advises caution in severe impairment—risk of accumulation

Renal impairment manufacturer advises caution in severe impairment—risk of accumulation

Pregnancy manufacturers advise avoid unless potential benefit outweighs risk (toxicity in animal studies); effective contraception required during treatment—consult product literature

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, diarrhoea, abdominal pain; headache, fatigue, fever, chills, depression; myalgia, arthralgia; rash, injection-site reactions; rarely confusion and systemic lupus erythematosus; also reported, neutropenia, thrombocytopenia, proteinuria and raised liver enzymes

Indications and dose

See notes above and under Preparations below

Immukin® (Boehringer Ingelheim) (PoM)

Injection, recombinant human interferon gamma-1b 200 micrograms/mL, net price 0.5-mL vial = £75.00

Dose

- By subcutaneous injection

Body surface area 0.5 m² or less 1.5 micrograms/kg 3 times a week

Body surface area greater than 0.5 m² 50 micrograms/m² 3 times a week

Not recommended for infant under 6 months with chronic granulomatous disease

Canakinumab

Canakinumab is a recombinant human monoclonal antibody that selectively inhibits interleukin-1beta

receptor binding. It is licensed for the treatment of cryopyrin-associated periodic syndromes, including severe forms of familial cold auto-inflammatory syndrome (or familial cold urticaria), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurological cutaneous and articular syndrome). These are rare inherited auto-inflammatory disorders. It is also licensed for active systemic juvenile idiopathic arthritis in children who have had an inadequate response to NSAIDs and systemic corticosteroids (section 10.1.3).

CANAKINUMAB

Cautions history of recurrent infection or predisposition to infection; monitor full blood count including neutrophil count before starting treatment, 1–2 months after starting treatment, and periodically thereafter; children should receive all recommended vaccinations (including pneumococcal and inactivated influenza vaccine) before starting treatment; avoid live vaccines unless potential benefit outweighs risk—consult product literature and section 14.1, p. 604 for further information

Tuberculosis Children should be evaluated for latent and active tuberculosis before starting treatment and monitored for signs and symptoms of tuberculosis during and after treatment

Contra-indications active infection (see also Cautions); neutropenia; leucopenia; concomitant use with tumour necrosis factor inhibitors (possible increased risk of infections)

Hepatic impairment no information available

Renal impairment limited information available but manufacturer advises no dose adjustment required

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk; effective contraception required during treatment and for up to 3 months after last dose

Breast-feeding consider if benefit outweighs risk—not known if present in human milk

Side-effects vertigo, malaise, increased susceptibility to infection (including serious infection), injection-site reactions, neutropenia, back pain; *less commonly* gastro-oesophageal reflux; *also reported* vomiting, malignancy

Indications and dose**Cryopyrin-associated periodic syndromes**

- By subcutaneous injection

Consult product literature

Active systemic juvenile idiopathic arthritis (in combination with methotrexate or alone) in children who have had an inadequate response to NSAIDs and systemic corticosteroids section 10.1.3

Ilaris® (Novartis) (PoM)

Injection, powder for reconstitution, canakinumab, net price 150-mg vial = £9927.80

Mifamurtide

Mifamurtide is licensed in children and adolescents for the treatment of high-grade, resectable, non-metastatic osteosarcoma after complete surgical resection. It is used in combination with chemotherapy.

NICE guidance**Mifamurtide for the treatment of osteosarcoma (October 2011)**

Mifamurtide in combination with postoperative multi-agent chemotherapy is recommended (within its licensed indication), as an option for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults and when mifamurtide is made available at a reduced cost to the NHS under the patient access scheme.

www.nice.org.uk/TA235

MIFAMURTIDE

Cautions asthma and chronic obstructive pulmonary disease—consider prophylactic bronchodilator therapy; history of autoimmune, inflammatory, or collagen disease; monitor renal function, hepatic function and clotting parameters; monitor patients with history of venous thrombosis, vasculitis, or unstable cardiovascular disorders for persistent or worsening symptoms during administration—consult product literature **interactions:** Appendix 1 (mifamurtide)

Hepatic impairment use with caution—no information available

Renal impairment use with caution—no information available

Pregnancy avoid; effective contraception required

Breast-feeding avoid—no information available

Side-effects gastro-intestinal disturbances (including anorexia, nausea, vomiting, diarrhoea, constipation, abdominal pain, dyspepsia); tachycardia, hypertension, palpitations, hypotension, phlebitis; oedema, respiratory disorders (including dyspnoea, epistaxis, cough, tachypnoea, haemoptysis, pleural effusion); confusion, depression, insomnia, headache, dizziness, paraesthesia, hypoaesthesia, tremor, drowsiness, anxiety; hypokalaemia, anaemia, leucopenia, thrombocytopenia, granulocytopenia; haematuria, dysuria, pollakiuria; musculoskeletal pain; blurred vision; vertigo, tinnitus, hearing loss; sweating, alopecia, rash, dry skin, flushing

Indications and dose

- See notes above
- By intravenous infusion (over 1 hour)
Consult local treatment protocols for details

Mepact[®] (Takeda) ▼ (PoM)

Intravenous infusion, powder for reconstitution, mifamurtide, net price 4-mg vial = £2375.00

8.3 Sex hormones and hormone antagonists in malignant disease

Classification not used in *BNF for Children*.

9 Nutrition and blood

9.1 Anaemias and some other blood disorders	448
9.1.1 Iron-deficiency anaemias	448
9.1.1.1 Oral iron	448
9.1.1.2 Parenteral iron	450
9.1.2 Drugs used in megaloblastic anaemias	452
9.1.3 Drugs used in hypoplastic, haemolytic, and renal anaemias	454
9.1.4 Drugs used in platelet disorders	460
9.1.5 G6PD deficiency	460
9.1.6 Drugs used in neutropenia	461
9.2 Fluids and electrolytes	463
9.2.1 Oral preparations for fluid and electrolyte imbalance	463
9.2.1.1 Oral potassium	464
9.2.1.2 Oral sodium and water	465
9.2.1.3 Oral bicarbonate	466
9.2.2 Parenteral preparations for fluid and electrolyte imbalance	467
9.2.2.1 Electrolytes and water	467
9.2.2.2 Plasma and plasma substitutes	471
9.3 Intravenous nutrition	472
9.4 Oral nutrition	474
9.4.1 Foods for special diets	474
9.4.2 Enteral nutrition	475
9.5 Minerals	477
9.5.1 Calcium and magnesium	477
9.5.1.1 Calcium supplements	477
9.5.1.2 Hypercalcaemia and hypercalciuria	479
9.5.1.3 Magnesium	479
9.5.2 Phosphorus	480
9.5.2.1 Phosphate supplements	480
9.5.2.2 Phosphate-binding agents	481
9.5.3 Fluoride	482
9.5.4 Zinc	483
9.6 Vitamins	484
9.6.1 Vitamin A	484
9.6.2 Vitamin B group	485
9.6.3 Vitamin C	486
9.6.4 Vitamin D	487
9.6.5 Vitamin E	490
9.6.6 Vitamin K	491

9.6.7 Multivitamin preparations	492
9.7 Bitters and tonics	493
9.8 Metabolic disorders	493
9.8.1 Drugs used in metabolic disorders	493
9.8.2 Acute porphyrias	502

9.1 Anaemias and some other blood disorders

9.1.1 Iron-deficiency anaemias
9.1.2 Drugs used in megaloblastic anaemias
9.1.3 Drugs used in hypoplastic, haemolytic, and renal anaemias
9.1.4 Drugs used in platelet disorders
9.1.5 G6PD deficiency
9.1.6 Drugs used in neutropenia

Before initiating treatment for anaemia it is essential to determine which type is present. Iron salts may be harmful and result in iron overload if given alone to patients with anaemias other than those due to iron deficiency.

9.1.1 Iron-deficiency anaemias

9.1.1.1 Oral iron
9.1.1.2 Parenteral iron

Treatment with an iron preparation is justified only in the presence of a demonstrable iron-deficiency state. Before starting treatment, it is important to exclude any serious underlying cause of the anaemia (e.g. gastro-intestinal bleeding). The possibility of thalassaemia should be considered in children of Mediterranean or Indian sub-continent descent.

Prophylaxis with an iron preparation may be appropriate in those with a poor diet, malabsorption, menorrhagia, pregnancy, in haemodialysis patients, and in the management of low birth-weight infants such as preterm neonates.

9.1.1.1 Oral iron

Iron salts should be given by mouth unless there are good reasons for using another route.

Ferrous salts show only marginal differences between one another in efficiency of absorption of iron. Haemoglobin regeneration rate is little affected by the type of salt used provided sufficient iron is given, and in most patients the speed of response is not critical. Choice of preparation is thus usually decided by formulation, palatability, incidence of side-effects, and cost.

Treatment of iron-deficiency anaemia The oral dose of **elemental iron** to treat deficiency is 3–6 mg/kg (max. 200 mg) daily given in 2–3 divided doses. Iron supplementation may also be required to produce an optimum response to erythropoietins in iron-deficient children with chronic renal failure or in preterm neonates. (See also Prophylaxis of iron deficiency, below.)

Prescribing Express the dose in terms of elemental iron and iron salt and select the most appropriate preparation; specify both the iron salt and formulation on the prescription. The iron content of artificial formula feeds should also be considered.

Iron content of different iron salts

Iron salt	Amount	Content of ferrous iron
Ferrous fumarate	200 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous sulfate	300 mg	60 mg
Ferrous sulfate, dried	200 mg	65 mg
Sodium ferredetate	190 mg	27.5 mg

Therapeutic response The haemoglobin concentration should rise by about 100–200 mg/100 mL (1–2 g/litre) per day or 2 g/100 mL (20 g/litre) over 3–4 weeks. When the haemoglobin is in the normal range, treatment should be continued for a further 3 months to replenish the iron stores. Epithelial tissue changes such as atrophic glossitis and koilonychia are usually improved, but the response is often slow. The most common reason for lack of response in children is poor compliance; poor absorption is rare in children.

Prophylaxis of iron deficiency In neonates, haemoglobin and haematocrit concentrations change rapidly. These changes are not due to iron deficiency and cannot be corrected by iron supplementation. Similarly, neonatal anaemia resulting from repeated blood sampling does not respond to iron therapy.

All babies, including preterm neonates, are born with substantial iron stores but these stores can become depleted unless dietary intake is adequate. All babies require an iron intake of 400–700 nanograms daily to maintain body stores. Iron in breast milk is well absorbed but that in artificial feeds or in cow's milk is less so. Most artificial formula feeds are sufficiently fortified with iron to prevent deficiency and their iron content should be taken into account when considering further iron supplementation.

Dose Prophylactic iron supplementation (elemental iron 5 mg daily) may be required in babies of low birth-weight who are solely breast-fed; supplementation is started 4–6 weeks after birth and continued until mixed feeding is established.

Infants with a poor diet may become anaemic in the second year of life, particularly if cow's milk, rather than fortified formula feed, is a major part of the diet.

Compound preparations Some oral preparations contain **ascorbic acid** to aid absorption of the iron, but the therapeutic advantage of such preparations is minimal and cost may be increased.

There is no justification for the inclusion of other ingredients, such as the **B group of vitamins**, except **folic acid** for pregnant women, see p. 452.

Side-effects Gastro-intestinal irritation can occur with iron salts. Nausea and epigastric pain are dose-related, but the relationship between dose and altered bowel habit (constipation or diarrhoea) is less clear. Oral iron can exacerbate diarrhoea in patients with inflammatory bowel disease.

Iron preparations taken orally can be constipating and occasionally lead to faecal impaction.

If side-effects occur, the dose may be reduced; alternatively, another iron salt may be used, but an improvement in tolerance may simply be a result of a lower content of elemental iron. The incidence of side-effects due to ferrous sulfate is no greater than with other iron salts when compared on the basis of equivalent amounts of elemental iron.

Iron preparations are an important cause of accidental overdose in children and as little as 20 mg/kg of elemental iron can lead to symptoms of toxicity. For the treatment of **iron overdose**, see Emergency Treatment of Poisoning, p. 29.

Counselling Although iron preparations are best absorbed on an empty stomach, they can be taken after food to reduce gastro-intestinal side-effects; they may discolour stools.

FERROUS SULFATE

Cautions interactions: Appendix 1 (iron)

Side-effects see notes above

Indications and dose

Iron-deficiency anaemia, prophylaxis of iron deficiency see notes above and preparations

Ferrous Sulfate (Non-proprietary)

Tablets, coated, dried ferrous sulfate 200 mg (65 mg iron), net price 28-tab pack = 97p
Dose

Child 6–18 years prophylactic, 1 tablet daily; therapeutic, 1 tablet 2–3 times daily, see notes above

Ironorm® Drops (Wallace Mfg)

Oral drops, ferrous sulfate 125 mg (25 mg iron)/mL, net price 15 mL = £28.00
Dose

Child 1 month–6 years prophylactic 0.3 mL daily, but see notes above

Child 6–18 years prophylactic 0.6 mL daily

FERROUS FUMARATE

Cautions interactions: Appendix 1 (iron)

Side-effects see notes above

Indications and dose

Iron-deficiency anaemia, prophylaxis of iron deficiency see notes above and preparations

Fersaday® (AMCo)

Tablets, brown, f/c, ferrous fumarate 322 mg (100 mg iron). Net price 28-tab pack = 95p
Dose

Child 12–18 years prophylactic, 1 tablet daily; therapeutic, 1 tablet twice daily

Ferrous Fumarate (Non-proprietary)

Tablets, ferrous fumarate 210 mg (68 mg iron), net price 84 = £2.30
Dose

Child 12–18 years prophylactic, 1 tablet 1–2 times daily; therapeutic, 1 tablet 2–3 times daily

Syrup, ferrous fumarate approx. 140 mg (45 mg iron)/5 mL, net price 200 mL = £3.73

Dose

Preterm neonate see notes above

Neonate see notes above

Child 1 month–12 years see notes above

Child 12–18 years prophylactic, 5 mL twice daily; therapeutic, 10 mL twice daily

Galfer® (Thornton & Ross)

Capsules, red/green, ferrous fumarate 305 mg (100 mg iron), net price 100 = £2.00

Dose

Child 12–18 years prophylactic, 1 capsule daily; therapeutic, 1 capsule twice daily

Syrup, brown, sugar-free ferrous fumarate 140 mg (45 mg iron)/5 mL. Net price 300 mL = £5.33

Dose

Preterm neonate and body-weight up to 3 kg prophylactic, 0.5 mL daily, see notes above

Neonate prophylactic and therapeutic, 0.25 mL/kg twice daily (total daily dose may alternatively be given in 3 divided doses), see notes above

Child 1 month–12 years prophylactic and therapeutic, 0.25 mL/kg twice daily (total daily dose may alternatively be given in 3 divided doses); max 20 mL daily, see notes above

Child 12–18 years prophylactic, 10 mL once daily; therapeutic, 10 mL 1–2 times daily

FERROUS GLUCONATE

Cautions interactions: Appendix 1 (iron)

Side-effects see notes above

Indications and dose

Iron-deficiency anaemia see notes above and preparation

Ferrous Gluconate (Non-proprietary)

Tablets, red, coated, ferrous gluconate 300 mg (35 mg iron), net price 28 = £1.95

Dose

Child 6–12 years prophylactic and therapeutic, 1–3 tablets daily

Child 12–18 years prophylactic, 2 tablets daily; therapeutic, 4–6 tablets daily in divided doses

POLYSACCHARIDE-IRON COMPLEX

Cautions interactions: Appendix 1 (iron)

Side-effects see notes above

Indications and dose

Iron-deficiency anaemia, prophylaxis of iron deficiency see notes above and preparation

Niferex® (Tillomed)

Elixir, brown, sugar-free, polysaccharide-iron complex equivalent to 100 mg of iron/5 mL. Net price 240-mL pack = £6.06; ¹30-mL dropper bottle for paediatric use = £2.16. Counselling, use of dropper

Dose

Neonate (from dropper bottle) 1 drop (approx. 500 micrograms iron) per 450 g body-weight 3 times daily, see notes above

Child 1 month–2 years (from dropper bottle) 1 drop (approx. 500 micrograms iron) per 450 g body-weight 3 times daily, see notes above

1. ¹except 30-mL paediatric dropper bottle for prophylaxis and treatment of iron deficiency in infants born prematurely; endorse prescription 'SL5'

Child 2–6 years therapeutic, 2.5 mL daily

Child 6–12 years therapeutic, 5 mL daily

Child 12–18 years prophylactic, 2.5 mL daily; therapeutic, 5 mL 1–2 times daily (5 mL once daily if required during second and third trimester of pregnancy)

SODIUM FEREDETATE

(Sodium ironedetate)

Cautions interactions: Appendix 1 (iron)

Side-effects see notes above

Licensed use not licensed for prophylaxis of iron deficiency

Indications and dose

Iron-deficiency anaemia, prophylaxis of iron deficiency see notes above and preparation

Sytiron® (Forum)

Elixir, sugar-free, sodium feredetate 190 mg equivalent to 27.5 mg of iron/5 mL. Net price 100 mL = £1.07

Dose

Neonate prophylactic, 1 mL daily, see notes above; therapeutic, up to 2.5 mL twice daily (smaller doses should be used initially), see notes above

Child 1 month–1 year prophylactic, 1 mL daily, see notes above; therapeutic, up to 2.5 mL twice daily (smaller doses should be used initially), see notes above

Child 1–5 years therapeutic, 2.5 mL 3 times daily

Child 5–12 years therapeutic, 5 mL 3 times daily

Child 12–18 years therapeutic, 5 mL increasing gradually to 10 mL 3 times daily

9.1.1.2 Parenteral iron

Iron can be administered parenterally as **iron dextran**, **iron sucrose**, or **ferric carboxymaltose**. Parenteral iron is generally reserved for use when oral therapy is unsuccessful because the child cannot tolerate oral iron, or does not take it reliably, or if there is continuing blood loss, or in malabsorption.

Many children with chronic renal failure who are receiving haemodialysis (and some who are receiving peritoneal dialysis) also require iron by the intravenous route on a regular basis (see also Erythropoietins, section 9.1.3).

With the exception of children with severe renal failure receiving haemodialysis, parenteral iron does not produce a faster haemoglobin response than oral iron provided that the oral iron preparation is taken reliably and is absorbed adequately. If parenteral iron is necessary, the dose should be calculated according to the child's body-weight and total iron deficit. Depending on the preparation used, parenteral iron is given as a total dose or in divided doses. Further treatment should be guided by monitoring haemoglobin and serum iron concentrations.

Anaphylactic reactions can occur with parenteral administration of iron complexes and facilities for cardiopulmonary resuscitation must be available—see MHRA/CHM advice, below. If children complain of acute symptoms particularly nausea, back pain, breath-

lessness, or develop hypotension, the infusion should be stopped.

MHRA/CHM advice

Serious hypersensitivity reactions with intravenous iron (August 2013)

Serious hypersensitivity reactions, including life-threatening and fatal anaphylactic reactions, have been reported in patients receiving intravenous iron. These reactions can occur even when a previous administration has been tolerated (including a negative test dose). Test doses are no longer recommended and caution is needed with *every* dose of intravenous iron.

Intravenous iron products should only be administered when appropriately trained staff and resuscitation facilities are immediately available; patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after every administration. In the event of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated.

The risk of hypersensitivity is increased in patients with known allergies, immune or inflammatory conditions, or those with a history of severe asthma, eczema, or other atopic allergy; in these patients, intravenous iron should only be used if the benefits outweigh the risks.

Intravenous iron should be avoided in the first trimester of pregnancy and used in the second or third trimesters only if the benefit outweighs the potential risks for both mother and fetus.

FERRIC CARBOXYMALTOSE

A ferric carboxymaltose complex containing 5% (50 mg/mL) of iron

Cautions hypersensitivity can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available (see MHRA/CHM advice, above); oral iron should not be given until 5 days after last injection; allergic disorders including asthma and eczema; infection (discontinue if ongoing bacteraemia)

Hepatic impairment use with caution; avoid in conditions where iron overload increases risk of impairment

Pregnancy avoid in first trimester; crosses the placenta in *animal* studies; may influence skeletal development

Side-effects gastro-intestinal disturbances; headache, dizziness; rash; injection-site reactions; *less commonly* hypotension, hypotension, flushing, chest pain, peripheral oedema, hypersensitivity reactions (including anaphylaxis), fatigue, paraesthesia, malaise, pyrexia, rigors, myalgia, arthralgia, back pain, pruritus, and urticaria; *rarely* dyspnoea

Licensed use not licensed for use in children under 14 years

Indications and dose

Iron-deficiency anaemia see notes above

- By slow intravenous injection or by intravenous infusion

Calculated according to body-weight and iron deficit, consult product literature

Ferinject® (Vifor) ▼ (PoM)

Injection, iron (as ferric carboxymaltose) 50 mg/mL, net price 2-mL vial = £19.10, 10-mL vial = £95.50, 20-mL vial = £181.45

Electrolytes Na⁺ 0.24 mmol/mL

IRON DEXTRAN

A complex of ferric hydroxide with sucrose containing 5% (50 mg/mL) of iron

Cautions hypersensitivity can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available (see MHRA/CHM advice, above); oral iron should not be given until 5 days after last injection

Contra-indications history of allergic disorders including asthma and eczema; infection; active rheumatoid arthritis

Hepatic impairment avoid in severe impairment

Renal impairment avoid in acute renal failure

Pregnancy avoid in first trimester

Side-effects *less commonly* nausea, vomiting, abdominal pain, flushing, dyspnoea, hypersensitivity reactions (including anaphylaxis), numbness, cramps, blurred vision, pruritus, and rash; *rarely* diarrhoea, chest pain, hypotension, angioedema, arrhythmias, tachycardia, dizziness, restlessness, fatigue, seizures, tremor, impaired consciousness, myalgia, arthralgia, sweating, and injection-site reactions; *very rarely* hypotension, palpitation, headache, paraesthesia, haemolysis, and transient deafness

Licensed use not licensed for use in children under 14 years

Indications and dose

Iron-deficiency anaemia see notes above

- By slow intravenous injection or by intravenous infusion

Calculated according to body-weight and iron deficit, consult product literature

CosmoFer® (Pharmacosmos) ▼ (PoM)

Injection, iron (as iron dextran) 50 mg/mL, net price 2-mL amp = £7.97; 10-mL amp = £39.85

IRON SUCROSE

A complex of ferric hydroxide with sucrose containing 2% (20 mg/mL) of iron

Cautions hypersensitivity reactions can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available (see MHRA/CHM advice, above); oral iron should not be given until 5 days after last injection; infection (discontinue if ongoing bacteraemia)

Contra-indications history of allergic disorders including asthma, eczema, and anaphylaxis

Hepatic impairment use with caution; avoid in conditions where iron overload increases risk of impairment

Pregnancy avoid in first trimester

Side-effects taste disturbances; *less commonly* nausea, vomiting, abdominal pain, diarrhoea, hypotension, tachycardia, flushing, palpitation, chest pain, bronchospasm, dyspnoea, headache, dizziness, fever, myalgia, pruritus, rash, and injection-site reactions; *rarely* peripheral oedema, hypotension, hypersensitivity reactions (including anaphylaxis), fatigue, asth-

enia, and paraesthesia; bradycardia, confusion, arthralgia, and increased sweating also reported

Licensed use not licensed for use in children

Indications and dose

Iron-deficiency anaemia see notes above

- **By slow intravenous injection or by intravenous infusion**

Calculated according to body-weight and iron deficit, consult product literature; each divided dose should not exceed 3 mg/kg/dose (or for body-weight over 67 kg, max. 200 mg/dose)

Venofer® (Vifor) ▼ (PoM)

Injection, iron (as iron sucrose) 20 mg/mL, net price 5-mL vial = £10.24

9.1.2 Drugs used in megaloblastic anaemias

Megaloblastic anaemias are rare in children; they may result from a lack of either vitamin B₁₂ or folate, and it is essential to establish in every case which deficiency is present and the underlying cause. In emergencies, when delay might be dangerous, it is sometimes necessary to administer both substances after the bone marrow test while plasma assay results are awaited. Normally, however, appropriate treatment should not be instituted until the results of tests are available.

Vitamin B₁₂ is used in the treatment of megaloblastosis caused by *prolonged nitrous oxide anaesthesia*, which inactivates the vitamin, and in the rare disorders of *congenital transcobalamin II deficiency*, *methylmalonic acidemia* and *homocystinuria* (see section 9.8.1).

Vitamin B₁₂ should be given prophylactically after *total ileal resection*.

Apart from dietary deficiency, all other causes of vitamin B₁₂ deficiency are attributable to malabsorption. There is little place for the use of low-dose vitamin B₁₂ orally and none for vitamin B₁₂ intrinsic factor complexes given by mouth. Vitamin B₁₂ in large oral doses [unlicensed] may be effective.

Hydroxocobalamin has completely replaced cyanocobalamin as the form of vitamin B₁₂ of choice for therapy; it is retained in the body longer than cyanocobalamin and thus for maintenance therapy can be given at intervals of up to 3 months. Treatment is generally initiated with frequent administration of intramuscular injections to replenish the depleted body stores. Thereafter, maintenance treatment, which is usually for life, can be instituted. There is no evidence that doses larger than those recommended provide any additional benefit in vitamin B₁₂ neuropathy.

Folic acid has few indications for long-term therapy since most causes of folate deficiency are self-limiting or will yield to a short course of treatment. It should not be used in undiagnosed megaloblastic anaemia unless vitamin B₁₂ is administered concurrently otherwise neuropathy may be precipitated (see above).

In *folate-deficient megaloblastic anaemia* (e.g. because of poor nutrition, pregnancy, or treatment with antiepileptics), daily folic acid supplementation for 4 months brings about haematological remission and replenishes body stores; higher doses may be necessary in malabsorption states. In pregnancy, folic acid 5 mg daily is continued to term.

For prophylaxis in *chronic haemolytic states*, *malabsorption* or in *renal dialysis*, folic acid is given daily or sometimes weekly, depending on the diet and the rate of haemolysis.

Folic acid is also used for the prevention of methotrexate-induced side-effects in juvenile idiopathic arthritis (see also section 10.1.3, p. 513), severe Crohn's disease (see section 1.5.3, p. 53), and severe psoriasis (see section 13.5.3, p. 578).

For *prophylaxis in pregnancy*, see Prevention of Neural Tube Defects below.

Folic acid is actively excreted in breast milk and is well absorbed by the infant. It is also present in cow's milk and artificial formula feeds but is heat labile. Serum and red cell folate concentrations fall after delivery and urinary losses are high, particularly in low birth-weight neonates. Although symptomatic deficiency is rare in the absence of malabsorption or prolonged diarrhoea, it is common for neonatal units to give supplements of folic acid to all preterm neonates from 2 weeks of age until full-term corrected age is reached, particularly if heated breast milk is used without an artificial formula fortifier.

Folinic acid is also effective in the treatment of folate-deficient megaloblastic anaemia but it is normally only used in association with cytotoxic drugs (see section 8.1); it is given as calcium folinate.

Prevention of neural tube defects Folic acid supplements taken before and during pregnancy can reduce the occurrence of neural tube defects. The risk of a neural tube defect occurring in a child should be assessed and folic acid given as follows:

Women at a low risk of conceiving a child with a neural tube defect should be advised to take folic acid as a medicinal or food supplement at a dose of 400 micrograms daily before conception and until week 12 of pregnancy. Women who have not been taking folic acid and who suspect they are pregnant should start at once and continue until week 12 of pregnancy.

Couples are at a high risk of conceiving a child with a neural tube defect if either partner has a neural tube defect (or either partner has a family history of neural tube defects), if they have had a previous pregnancy affected by a neural tube defect, or if the woman has coeliac disease (or other malabsorption state), diabetes mellitus, sickle-cell anaemia, or is taking antiepileptic medicines (see also section 4.8.1).

Women in the high-risk group who wish to become pregnant (or who are at risk of becoming pregnant) should be advised to take folic acid 5 mg daily and continue until week 12 of pregnancy (women with sickle-cell disease should continue taking their normal dose of folic acid 5 mg daily (or increase the dose to 5 mg daily) and continue this throughout pregnancy).

There is **no** justification for prescribing multiple-ingredient vitamin preparations containing vitamin B₁₂ or folic acid.

HYDROXOCOBALAMIN

Cautions should not be given before diagnosis fully established but see also notes above; **interactions** Appendix 1 (hydroxocobalamin)

Breast-feeding present in milk but not known to be harmful

Side-effects nausea, headache, dizziness; fever, hypersensitivity reactions (including rash and pruritus); injection-site reactions; hypokalaemia and thrombocytosis during initial treatment; chromaturia

Licensed use licensed for use in children (age not specified by manufacturers); not licensed for use in inborn errors of metabolism

Indications and dose

Macrocytic anaemia without neurological involvement

- By intramuscular injection

Child 1 month–18 years initially 250 micrograms–1 mg 3 times a week for 2 weeks then 250 micrograms once weekly until blood count normal, then 1 mg every 3 months

Macrocytic anaemia with neurological involvement

- By intramuscular injection

Child 1 month–18 years initially 1 mg on alternate days until no further improvement, then 1 mg every 2 months

Prophylaxis of macrocytic anaemias associated with vitamin B₁₂ deficiency

- By intramuscular injection

Child 1 month–18 years 1 mg every 2–3 months

Leber's optic atrophy

- By intramuscular injection

Initially 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, thereafter 1 mg every 1–3 months

Congenital transcobalamin II deficiency

- By intramuscular injection

Neonate 1 mg 3 times a week, reduce after 1 year to 1 mg once weekly or as appropriate

Child 1 month–18 years 1 mg 3 times a week, reduce after 1 year to 1 mg once weekly or as appropriate

Methylmalonic acidemia and homocystinuria

- By intramuscular injection

Child 1 month–18 years initially 1 mg daily for 5–7 days, reduce according to response to maintenance dose of up to 1 mg once or twice weekly

Methylmalonic acidemia, maintenance once intramuscular response established

- By mouth

Child 1 month–18 years 5–10 mg once or twice weekly



Note Some children do not respond to the oral route

Cyanide poisoning

See Emergency Treatment of Poisoning, p. 31

Hydroxocobalamin (Non-proprietary) PoM

Injection, hydroxocobalamin 1 mg/mL. Net price 1-mL amp = 73p

Brands include Cobalin-H[®] , Neo-Cytamen[®] 

Injection, hydroxocobalamin 2.5 mg/mL, 2 mL. Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Administration For administration *by mouth*, injection solution may be given orally; it will not have prolonged effect via this route

Note The BP directs that when Vitamin B₁₂ injection is prescribed or demanded hydroxocobalamin injection shall be dispensed or supplied

Powder available from specialist importing companies

FOLIC ACID

Cautions should never be given alone for vitamin B₁₂ deficiency states (may precipitate subacute combined degeneration of the spinal cord); **interactions**:

Appendix 1 (folates)

Side-effects rarely gastro-intestinal disturbances

Licensed use unlicensed for limiting methotrexate toxicity

Indications and dose

Folate supplementation in neonates (see notes above)

- By mouth

Neonate 50 micrograms once daily or 500 micrograms once weekly

Megaloblastic anaemia due to folate deficiency (see notes above)

- By mouth

Neonate initially 500 micrograms/kg once daily for up to 4 months

Child 1 month–1 year initially 500 micrograms/kg once daily (max. 5 mg) for up to 4 months; up to 10 mg daily may be required in malabsorption states

Child 1–18 years 5 mg daily for 4 months (until term in pregnant women); up to 15 mg daily may be required in malabsorption states

Haemolytic anaemia; metabolic disorders

- By mouth

Child 1 month–12 years 2.5–5 mg once daily

Child 12–18 years 5–10 mg once daily

Prophylaxis of folate deficiency in dialysis

- By mouth

Child 1 month–12 years 250 microgram/kg (max. 10 mg) once daily

Child 12–18 years 5–10 mg once daily

Prevention of methotrexate side-effects in juvenile idiopathic arthritis

- By mouth

Child 2–18 years 1 mg daily or 5 mg once weekly, adjusted according to local guidelines

Prevention of methotrexate side-effects in severe Crohn's disease or severe psoriasis

- By mouth

See section 1.5.3 and section 13.5.3

Prevention of neural tube defects

- By mouth

See notes above

Folic Acid (Non-proprietary) (PoM)

Tablets, folic acid 400 micrograms, net price 90-tab pack = £2.71; 5 mg, 28-tab pack = 91p

Syrup, folic acid 2.5 mg/5 mL, net price 150 mL = £9.16

Brands include Lexpec® (sugar-free)

9.1.3 Drugs used in hypoplastic, haemolytic, and renal anaemias

Anabolic steroids (see BNF, section 6.4.3), pyridoxine, antilymphocyte immunoglobulin, and various corticosteroids are used in hypoplastic and haemolytic anaemias.

Antilymphocyte immunoglobulin given intravenously through a central line over 12–18 hours each day for 5 days produces a response in about 50% of cases of acquired *aplastic anaemia*; the response rate may be increased when ciclosporin is given as well. Severe reactions are common in the first 2 days and profound immunosuppression can occur; antilymphocyte immunoglobulin should be given under specialist supervision with appropriate resuscitation facilities. Alternatively, oxymetholone tablets (available from 'special-order' manufacturers or specialist importing companies, see p. 840) may be used in aplastic anaemia at a dose of 1–5 mg/kg daily for 3 to 6 months.

It is unlikely that dietary deficit of **pyridoxine** (section 9.6.2) produces clinically relevant haematological effects. However, certain forms of *sideroblastic anaemia* respond to pharmacological doses, possibly reflecting its role as a co-enzyme during haemoglobin synthesis. Pyridoxine is indicated in both *idiopathic acquired* and *hereditary sideroblastic anaemias*. Although complete cures have not been reported, some increase in haemoglobin can occur with high doses. *Reversible sideroblastic anaemias* respond to treatment of the underlying cause but pyridoxine is indicated in pregnancy, haemolytic anaemias, or during isoniazid treatment.

Corticosteroids (section 6.3) have an important place in the management of haematological disorders including *autoimmune haemolytic anaemia*, *idiopathic thrombocytopenias* (section 9.1.4) and *neutropenias*, and *major transfusion reactions*. They are also used in chemotherapy schedules for many types of *lymphoma*, *lymphoid leukaemias*, and *paraproteinaemias*, including *multiple myeloma*.

Erythropoietins

Epoetins (recombinant human erythropoietins) are used to treat the anaemia associated with erythropoietin deficiency in chronic renal failure, see below.

Epoetin beta is also used for the prevention of anaemia in preterm neonates of low birth-weight; a therapeutic response may take several weeks. Only unpreserved formulations should be used as other preparations may contain benzyl alcohol (see Excipients, p. 2).

There is insufficient information to support the use of erythropoietins in children with leukaemia or in those receiving cancer chemotherapy.

Darbepoetin is a glycosylated derivative of epoetin; it persists longer in the body and can be administered less frequently than epoetin.

Other factors, such as iron or folate deficiency, that contribute to the anaemia of chronic renal failure should be corrected before treatment and monitored during therapy. Supplemental iron may improve the response in resistant patients and in preterm neonates (see section 9.1.1.1). Aluminium toxicity, concurrent infection, or other inflammatory disease can impair the response to erythropoietin.

Erythropoietins—haemoglobin concentration

In chronic kidney disease, the use of erythropoietins can be considered in a child with anaemia. The aim of treatment is to relieve symptoms of anaemia and to avoid the need for blood transfusion. The optimum haemoglobin concentration is dependent on the child's age and factors such as symptoms, comorbidities, and patient preferences. The haemoglobin concentration should not be increased beyond that which provides adequate control of symptoms of anaemia. In *adults*, overcorrection of haemoglobin concentration with erythropoietins in those with chronic kidney disease may increase the risk of serious cardiovascular events and death; haemoglobin concentrations higher than 12 g/100 mL should be avoided in children.

For MHRA/CHM advice relating to adults, see BNF section 9.1.3.

Pure red cell aplasia

There have been very rare reports of pure red cell aplasia in patients treated with erythropoietins. In patients who develop a lack of efficacy with erythropoietin therapy and with a diagnosis of pure red cell aplasia, treatment with erythropoietins must be discontinued and testing for erythropoietin antibodies considered. Patients who develop pure red cell aplasia should not be switched to another form of erythropoietin.

DARBEPOETIN ALFA

Cautions see Epoetin

Contra-indications see Epoetin

Hepatic impairment manufacturer advises caution

Pregnancy no evidence of harm in *animal studies*—manufacturer advises caution

Breast-feeding manufacturer advises avoid—no information available

Side-effects see Epoetin; also, oedema, injection-site pain; isolated reports of pure red cell aplasia particularly following subcutaneous administration in patients with chronic renal failure (discontinue therapy)—see also notes above

Indications and dose

Symptomatic anaemia associated with chronic renal failure in children on dialysis (see also notes above)

• **By intravenous or subcutaneous injection**

Child 11–18 years initially 450 nanograms/kg once weekly adjusted according to response by approx. 25% at intervals of at least 4 weeks; maintenance dose, given once weekly or once every 2 weeks

1. Can be sold to the public provided daily doses do not exceed 500 micrograms

Symptomatic anaemia associated with chronic renal failure in children not on dialysis (see also notes above)

• By intravenous or subcutaneous injection

Child 11–18 years by *subcutaneous* or *intravenous injection*, initially 450 nanograms/kg once weekly or by *subcutaneous injection*, initially 750 nanograms/kg once every 2 weeks; adjusted according to response by approx. 25% at intervals of at least 4 weeks; maintenance dose, given *subcutaneously* or *intravenously* once weekly or *subcutaneously* once every 2 weeks or *subcutaneously* once every month

Note Subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. When changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements. Adjust doses not more frequently than every 2 weeks during maintenance treatment.

Aranesp® (Amgen) (PoM)

Injection, prefilled syringe, darbepoetin alfa, 25 micrograms/mL, net price 0.4 mL (10 micrograms) = £14.68; 40 micrograms/mL, 0.375 mL (15 micrograms) = £22.02, 0.5 mL (20 micrograms) = £29.36; 100 micrograms/mL, 0.3 mL (30 micrograms) = £44.04, 0.4 mL (40 micrograms) = £58.73, 0.5 mL (50 micrograms) = £73.41; 200 micrograms/mL, 0.3 mL (60 micrograms) = £88.09, 0.4 mL (80 micrograms) = £117.45, 0.5 mL (100 micrograms) = £146.81, 0.65 mL (130 micrograms) = £190.86; 500 micrograms/mL, 0.3 mL (150 micrograms) = £220.22, 0.6 mL (300 micrograms) = £440.43, 1 mL (500 micrograms) = £734.05

Injection (Aranesp® SureClick), prefilled disposable injection device, darbepoetin alfa, 40 micrograms/mL, net price 0.5 mL (20 micrograms) = £29.36; 100 micrograms/mL, net price 0.4 mL (40 micrograms) = £58.72; 200 micrograms/mL, net price 0.3 mL (60 micrograms) = £88.09, 0.4 mL (80 micrograms) = £117.45, 0.5 mL (100 micrograms) = £146.81; 500 micrograms/mL, net price 0.3 mL (150 micrograms) = £220.22, 0.6 mL (300 micrograms) = £440.43, 1 mL (500 micrograms) = £734.05

EPOETIN ALFA, BETA, and ZETA (Recombinant human erythropoietins)

Note The prescriber must specify which epoetin is required, see also Biosimilar medicines, p. 2

Cautions see notes above; also inadequately treated or poorly controlled blood pressure (monitor closely blood pressure, reticulocyte counts, haemoglobin, and electrolytes), interrupt treatment if blood pressure uncontrolled; sudden stabbing migraine-like pain is warning of hypertensive crisis; sickle-cell disease (lower target haemoglobin concentration may be appropriate); ischaemic vascular disease; thrombocytosis (monitor platelet count for first 8 weeks); epilepsy; malignant disease; increase in unfractionated or low molecular weight heparin dose may be needed during dialysis

Contra-indications pure red cell aplasia following erythropoietin therapy (see also notes above);

uncontrolled hypertension; avoid injections containing benzyl alcohol in neonates (see under preparations, below)

Hepatic impairment manufacturers advise caution in chronic hepatic failure

Pregnancy no evidence of harm; benefits probably outweigh risks of anaemia and blood transfusion

Breast-feeding unlikely to be present in milk; effect on infant minimal

Side-effects diarrhoea, nausea, vomiting; dose-dependent increase in blood pressure or aggravation of hypertension; in isolated patients with normal or low blood pressure, hypertensive crisis with encephalopathy-like symptoms and generalised tonic-clonic seizures requiring immediate medical attention; dose-dependent increase in platelet count (but thrombocytosis rare) regressing during treatment; influenza-like symptoms (may be reduced if intravenous injection given over 5 minutes); cardiovascular events; shunt thrombosis especially if tendency to hypotension or arteriovenous shunt complications; *very rarely* sudden loss of efficacy because of pure red cell aplasia, particularly following subcutaneous administration in patients with chronic renal failure (discontinue erythropoietin therapy)—see also notes above, hyperkalaemia, hypersensitivity reactions (including anaphylaxis and angioedema), skin reactions, injection-site reactions, and peripheral oedema also reported

Licensed use *Eprex*® 20 000–unit, 30 000–unit, and 40 000–unit prefilled syringes not licensed for use in children

Indications and dose

See under preparations, below

▲ **Epoetin alfa**

Binocrit® (Sandoz) (PoM)

Injection, prefilled syringe, epoetin alfa, net price 1000 units = £4.33; 2000 units = £8.65; 3000 units = £12.98; 4000 units = £17.31; 5000 units = £21.64; 6000 units = £25.96; 8000 units = £40.73; 10 000 units = £43.27

Note Biosimilar Medicine, p. 2

Dose

Symptomatic anaemia associated with chronic renal failure in children on haemodialysis (see also notes above)

• By intravenous injection over 1–5 minutes

Child 1 month–18 years initially 50 units/kg 3 times weekly adjusted according to response in steps of 25 units/kg 3 times weekly at intervals of at least 4 weeks; maintenance dose, body-weight under 10 kg usually 75–150 units/kg 3 times weekly, body-weight 10–30 kg usually 60–150 units/kg 3 times weekly, body-weight over 30 kg usually 30–100 units/kg 3 times weekly

Note Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Eprex® (Janssen) (PoM)

Injection, prefilled syringe, epoetin alfa, net price 1000 units = £5.53; 2000 units = £11.06; 3000 units = £16.59; 4000 units = £22.12; 5000 units = £27.65; 6000 units = £33.19; 8000 units = £44.25; 10 000 units = £55.31; 20 000 units = £110.62; 30 000 units = £199.11; 40 000 units = £265.48. An auto-injector device is available for use with prefilled syringes

Dose

Symptomatic anaemia associated with chronic renal failure in children on haemodialysis (see also notes above)

- By intravenous injection over 1–5 minutes

Child 1 month–18 years initially 50 units/kg 3 times weekly adjusted according to response in steps of 25 units/kg 3 times weekly at intervals of at least 4 weeks; maintenance dose, body-weight under 10 kg usually 75–150 units/kg 3 times weekly, body-weight 10–30 kg usually 60–150 units/kg 3 times weekly, body-weight 30–60 kg usually 30–100 units/kg 3 times weekly, body-weight over 60 kg usually 75–300 units/kg weekly (as a single dose or in divided doses)

Note Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

■ Epoetin beta

NeoRecormon® (Roche) (PoM)

Injection, prefilled syringe, epoetin beta, net price 500 units = £3.51; 2000 units = £14.03; 3000 units = £21.04; 4000 units = £28.06; 5000 units = £35.07; 6000 units = £42.08; 10 000 units = £70.14; 20 000 units = £140.29; 30 000 units = £210.43

Excipients include phenylalanine up to 300 micrograms/syringe (section 9.4.1)

Dose

Symptomatic anaemia associated with chronic renal failure (see also notes above)

- By subcutaneous injection

Neonate initially 20 units/kg 3 times weekly for 4 weeks, increased according to response at intervals of 4 weeks in steps of 20 units/kg 3 times weekly; total weekly dose may be divided into daily doses; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks; total weekly maintenance dose may be given as a single dose or in 3 or 7 divided doses; max. 720 units/kg weekly

Child 1 month–18 years initially 20 units/kg 3 times weekly for 4 weeks, increased according to response at intervals of 4 weeks in steps of 20 units/kg 3 times weekly; total weekly dose may be divided into daily doses; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks; total weekly maintenance dose may be given as a single dose or in 3 or 7 divided doses; max. 720 units/kg weekly

- By intravenous injection over 2 minutes

Neonate initially 40 units/kg 3 times weekly for 4 weeks, increased according to response to 80 units/kg 3 times weekly after 4 weeks, with further increases if needed at intervals of 4 weeks in steps of 20 units/kg 3 times weekly; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks; max. 720 units/kg weekly

Child 1 month–18 years initially 40 units/kg 3 times weekly for 4 weeks, increased according to response to 80 units/kg 3 times weekly after 4 weeks, with further increases if needed at intervals of 4 weeks in steps of 20 units/kg 3 times weekly; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks; max. 720 units/kg weekly

Note Subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Prevention of anaemias of prematurity in neonates with birth-weight of 0.75–1.5 kg and corrected gestational age under 34 weeks

- By subcutaneous injection (of single-dose, unpreserved injection)

Neonate 250 units/kg 3 times weekly preferably starting within 3 days of birth and continued for 6 weeks

Multidose injection, powder for reconstitution, epoetin beta, net price 50 000-unit vial = £374.48 (with solvent)

Excipients include phenylalanine up to 5 mg/vial (section 9.4.1), benzyl alcohol (avoid in neonates, see Excipients p. 2)

Note Avoid contact of reconstituted injection with glass; use only plastic materials

Dose

Symptomatic anaemia associated with chronic renal failure (see also notes above)

- By subcutaneous injection

Child 3–18 years initially 20 units/kg 3 times weekly for 4 weeks, increased according to response at intervals of 4 weeks in steps of 20 units/kg 3 times weekly; total weekly dose may be divided into daily doses; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks; total weekly maintenance dose may be given as a single dose or in 3 or 7 divided doses; max. 720 units/kg weekly

- By intravenous injection over 2 minutes

Child 3–18 years initially 40 units/kg 3 times weekly for 4 weeks, increased according to response to 80 units/kg 3 times weekly after 4 weeks, with further increases if needed at intervals of 4 weeks in steps of 20 units/kg 3 times weekly; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks; max. 720 units/kg weekly

Note Subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

■ Epoetin zeta

Retacrit® (Hospira) (PoM)

Injection, prefilled syringe, epoetin zeta, net price 1000 units = £5.66; 2000 units = £11.31; 3000 units = £16.97; 4000 units = £22.63; 5000 units = £28.28; 6000 units = £33.94; 8000 units = £45.25; 10 000 units = £56.57; 20 000 units = £113.13; 30 000 units = £169.70; 40 000 units = £226.26

Excipients include phenylalanine up to 500 micrograms/syringe (section 9.4.1)

Note Biosimilar Medicine, p. 2

Dose

Symptomatic anaemia associated with chronic renal failure in children on haemodialysis (see also notes above)

- By intravenous injection over 1–5 minutes

Child 1 month–18 years initially 50 units/kg 3 times weekly adjusted according to response in steps of 25 units/kg 3 times weekly at intervals of at least 4 weeks; maintenance dose, body-weight under 10 kg usually 75–150 units/kg 3 times weekly, body-weight 10–30 kg usually 60–150 units/kg 3 times weekly, body-weight over 30 kg usually 30–100 units/kg 3 times weekly

Note Avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks

Sickle-cell disease

Sickle-cell disease is caused by a structural abnormality of haemoglobin resulting in deformed, less flexible red blood cells. Acute complications in the more severe

forms include *sickle-cell crisis*, where infarction of the microvasculature and blood supply to organs results in severe pain. Sickle-cell crisis requires hospitalisation, intravenous fluids, analgesia (section 4.7), and treatment of any concurrent infection. Chronic complications include skin ulceration, renal failure, and increased susceptibility to infection. Pneumococcal vaccine (section 14.4), haemophilus influenzae type b vaccine (section 14.4), an annual influenza vaccine (section 14.4), and prophylactic penicillin (Table 2, section 5.1) reduce the risk of infection. Hepatitis B vaccine (section 14.4) should be considered if the child is not immune.

In most forms of sickle-cell disease, varying degrees of haemolytic anaemia are present accompanied by increased erythropoiesis; this may increase folate requirements and folate supplementation may be necessary (section 9.1.2).

Hydroxycarbamide can reduce the frequency of crises and the need for blood transfusions. Hydroxycarbamide should be considered, in consultation with a specialist centre, for children who have recurrent episodes of acute pain (more than 3 admissions in the previous 12 months, or who are very symptomatic in the community) or who have had 2 or more episodes of acute sickle chest syndrome in the last 2 years (or 1 episode requiring ventilatory support). Beneficial effects of hydroxycarbamide may not become evident for several months. Myelosuppression, and skin reactions are the most common side-effects.

HYDROXYCARBAMIDE

(Hydroxyurea)

Cautions see section 8.1 and notes above; also monitor renal and hepatic function before and during treatment; monitor full blood count before treatment, then every 2 weeks for the first 2 months and then every 2 months thereafter (or every 2 weeks if on max. dose); leg ulcers (review treatment if cutaneous vascular ulcerations develop); **interactions:** Appendix 1 (hydroxycarbamide)

Hepatic impairment manufacturer advises caution in mild to moderate impairment; avoid in severe impairment

Renal impairment reduce initial dose by 50% if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy avoid (teratogenic in animal studies); manufacturer advises effective contraception before and during treatment; see also section 8.1

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; also headache; less commonly dizziness, and rash; rarely reduced sperm count and activity; fever, amenorrhoea, bleeding, and hypomagnesaemia also reported

Indications and dose

Sickle-cell disease (see notes above)

• By mouth

Child 2–18 years initially 10–15 mg/kg once daily, increased every 12 weeks in steps of 2.5–5 mg/kg daily according to response; usual dose 15–30 mg/kg daily (max. 35 mg/kg daily)

Siklos® (Nordic) (PoM)

Tablets, scored, f/c, hydroxycarbamide 100 mg, net price 60-tab pack = £100.00; 1 g, 30-tab pack = £500.00

Iron overload

Severe tissue iron overload can occur in aplastic and other refractory anaemias, mainly as the result of repeated blood transfusions. It is a particular problem in refractory anaemias with hyperplastic bone marrow, especially *thalassaemia major*, where excessive iron absorption from the gut and inappropriate iron therapy can add to the tissue siderosis.

Iron overload associated with haemochromatosis can be treated with repeated venesection. Venesection may also be used for patients who have received multiple transfusions and whose bone marrow has recovered. Where venesection is contra-indicated, and in thalassaemia, the long-term administration of the iron chelating compound **desferrioxamine mesilate** is useful. Subcutaneous infusions of desferrioxamine are given over 8–12 hours, 3–7 times a week; the dose should reflect the degree of iron overload. The initial dose should not exceed 30 mg/kg. For established overload the dose is usually between 20 and 50 mg/kg daily. Desferrioxamine (up to 2 g per unit of blood) may also be given at the time of blood transfusion, provided that the desferrioxamine is **not** added to the blood and is **not** given through the same line as the blood (but the two may be given through the same cannula).

Iron excretion induced by desferrioxamine is enhanced by ascorbic acid (vitamin C, section 9.6.3) 100–200 mg daily by mouth; it should be given separately from food since it also enhances iron absorption. Ascorbic acid should not be given to children with cardiac dysfunction; in children with normal cardiac function ascorbic acid should be introduced 1 month after starting desferrioxamine.

Desferrioxamine infusion can be used to treat *aluminium overload* in dialysis patients; theoretically 100 mg of desferrioxamine binds with 4.1 mg of aluminium.

Deferasirox, an oral iron chelator, is licensed for the treatment of chronic iron overload in children over 6 years with thalassaemia major who receive frequent blood transfusions (more than 7 mL/kg/month of packed red blood cells). It is also licensed for transfusion-related chronic iron overload when desferrioxamine is contra-indicated or inadequate in children aged 2–5 years with thalassaemia major who receive frequent blood transfusions, children over 2 years with thalassaemia major who receive infrequent blood transfusions (less than 7 mL/kg/month of packed red blood cells), and in children over 2 years with other anaemias. Deferasirox is also licensed for the treatment of chronic iron overload when desferrioxamine is contra-indicated or inadequate in children over 10 years with non-transfusion-dependent thalassaemia syndromes.

The *Scottish Medicines Consortium* (p. 3) has advised (January 2007) that deferiasirox is accepted for restricted use within NHS Scotland for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions. It is not recommended for patients with myelodysplastic syndromes.

Deferiprone, an oral iron chelator, is licensed for the treatment of iron overload in children over 6 years of age with thalassaemia major in whom desferrioxamine is contra-indicated or is inadequate. Blood dyscrasias, particularly agranulocytosis, has been reported with deferiprone.

DEFERASIROX

Cautions eye and ear examinations required before treatment and annually during treatment; monitor body-weight, height and sexual development annually; monitor serum-ferritin concentration monthly; risk of gastro-intestinal ulceration and haemorrhage; platelet count less than 50×10^9 /litre; consider treatment interruption if unexplained cytopenia occurs; not recommended in conditions which may reduce life expectancy (e.g. high-risk myelodysplastic syndromes); history of liver cirrhosis; test liver function before treatment, then every 2 weeks during the first month, and then monthly; measure baseline serum-creatinine and monitor renal function weekly during the first month of treatment and monthly thereafter; test for proteinuria monthly; monitor liver-iron concentration every three months in children with non-transfusion-dependent thalassaemia syndromes when serum ferritin is < 800 micrograms/litre; **interactions:** Appendix 1 (deferasirox)

Hepatic impairment use with caution in moderate impairment, reduce dose considerably then gradually increase to max. 50% of normal dose; avoid in severe impairment

Renal impairment reduce dose by 10 mg/kg if serum-creatinine increased above age-appropriate limits or estimated glomerular filtration rate less than 90 mL/minute/1.73 m² on 2 consecutive occasions—interrupt treatment if deterioration in renal function persists after dose reduction; avoid if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid unless essential—toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects gastro-intestinal disturbances (including ulceration and fatal haemorrhage); headache; proteinuria; pruritus, rash; *less commonly* oedema, hepatitis, cholelithiasis, fatigue, anxiety, sleep disorder, dizziness, pyrexia, pharyngitis, glucosuria, renal tubulopathy, disturbances of hearing and vision (including lens opacity and maculopathy), and skin pigmentation; hepatic failure, acute renal failure, tubulointerstitial nephritis, blood disorders (including anaemia, agranulocytosis, neutropenia, pancytopenia, and thrombocytopenia), hypersensitivity reactions (including anaphylaxis and angioedema), and alopecia also reported

Licensed use see notes above

Indications and dose**Transfusion-related chronic iron overload**• **By mouth**

Child 2–18 years initially 10–30 mg/kg once daily according to serum-ferritin concentration and amount of transfused blood (consult product literature); maintenance, adjust dose every 3–6 months in steps of 5–10 mg/kg according to serum-ferritin concentration; usual max. 30 mg/kg daily, but may be increased to max. 40 mg/kg daily and reduced in steps of 5–10 mg/kg once control achieved

Chronic iron overload in non-transfusion-dependent thalassaemia syndromes• **By mouth**

Child 10–18 years initially 10 mg/kg once daily; adjust dose according to serum-ferritin concentration and liver-iron concentration (consult product literature); max. 10 mg/kg daily

Exjade® (Novartis) ▼ (PoM)

Dispersible tablets, deferasirox 125 mg, net price 28-tab pack = £117.60; 250 mg, 28-tab pack = £235.20; 500 mg, 28-tab pack = £470.40. Label: 13, 22, counselling, administration

Counselling Tablets should be dispersed in water, orange juice, or apple juice; if necessary, resuspend residue and swallow

DEFERIPRONE

Cautions monitor neutrophil count weekly and discontinue treatment if neutropenia develops; **interactions:** Appendix 1 (deferiprone)

Blood disorders Patients or their carers should be told how to recognise signs of neutropenia and advised to seek immediate medical attention if symptoms such as fever or sore throat develop

Contra-indications history of agranulocytosis or recurrent neutropenia

Hepatic impairment manufacturer advises monitor liver function—interrupt treatment if persistent elevation in serum alanine aminotransferase

Renal impairment manufacturer advises caution—no information available

Pregnancy manufacturer advises avoid before intended conception and during pregnancy—teratogenic and embryotoxic in *animal* studies; contraception advised in girls of child-bearing potential

Breast-feeding manufacturer advises avoid—no information available

Side-effects gastro-intestinal disturbances (reducing dose and increasing gradually may improve tolerance), increased appetite; headache; red-brown urine discoloration; neutropenia, agranulocytosis; zinc deficiency; arthropathy

Licensed use see notes above

Indications and dose**Iron overload in thalassaemia major**• **By mouth**

Child 6–18 years 25 mg/kg 3 times daily (max. 100 mg/kg daily)

Ferriprox® (Swedish Orphan) (PoM)

Tablets, f/c, scored, deferiprone 500 mg, net price 100-tab pack = £152.39; 1 g, 50-tab pack = £175.25. Label: 14, counselling, blood disorders

Oral solution, red, deferiprone 100 mg/mL, net price 500 mL = £152.39. Label: 14, counselling, blood disorders

DESFERIOXAMINE MESILATE
(Deferoxamine Mesilate)

Cautions eye and ear examinations before treatment and at 3-month intervals during treatment; monitor body-weight and height in children at 3-month intervals—risk of growth restriction with excessive doses; aluminium-related encephalopathy (may exacerbate neurological dysfunction); **interactions:** Appendix 1 (desferrioxamine)

Renal impairment use with caution

Pregnancy teratogenic in *animal* studies, manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises use only if potential benefit outweighs risk—no information available

Side-effects nausea, vomiting, abdominal pain, headache, pyrexia, growth retardation and bone disorders (see Cautions), arthralgia, myalgia, hearing disturbances, injection-site reactions; *rarely* diarrhoea, hepatic impairment, hypotension (especially when given too rapidly by intravenous injection), anaphylaxis, Yersinia and mucormycosis infections, blood dyscrasias (including thrombocytopenia and leucopenia), leg cramps, bone pain, visual disturbances (including lens opacity and retinopathy), rash; *very rarely* acute respiratory distress, neurological disturbances (including dizziness, neuropathy, convulsions, and paraesthesia), renal impairment; muscle spasms also reported

Indications and dose

Chronic iron overload see notes above

Aluminium overload in dialysis patients

- By intravenous infusion

Child 1 month–18 years 5 mg/kg once weekly

Iron poisoning

See Emergency Treatment of Poisoning, p. 29

Administration For *intravenous or subcutaneous infusion*, reconstitute powder with Water for Injection to a concentration of 100 mg/mL; dilute with Glucose 5% or Sodium Chloride 0.9%. In *haemodialysis or haemofiltration* administer over the last hour of dialysis (may be given via the dialysis fistula). *Intraperitoneal*: may be added to dialysis fluid. In CAPD give prior to the last exchange of the day.

Note For full details and warnings relating to administration, consult product literature

Desferrioxamine mesilate (Non-proprietary) PoM

Injection, powder for reconstitution, desferrioxamine mesilate, net price 500-mg vial = £4.26; 2-g vial = £17.65

Desferal® (Novartis) PoM

Injection, powder for reconstitution, desferrioxamine mesilate, net price 500-mg vial = £4.67; 2-g vial = £18.66

Atypical haemolytic uraemic syndrome and paroxysmal nocturnal haemoglobinuria

Eculizumab, a recombinant monoclonal antibody, inhibits terminal complement activation at the C5 protein and thereby reduces haemolysis and thrombotic microangiopathy. Eculizumab is used to reduce thrombotic microangiopathy in atypical haemolytic uraemic syndrome (aHUS). Eculizumab is also used in adults to reduce haemolysis in paroxysmal nocturnal haemoglobinuria (PNH), a severe and disabling form of haemolytic anaemia [unlicensed indication in children].

ECULIZUMAB

Cautions active systemic infection; monitor child for 1 hour after infusion; for *atypical haemolytic uraemic syndrome*, monitor for thrombotic microangiopathy

(measure platelet count, serum-lactate dehydrogenase concentration, and serum creatinine) during treatment and for at least 12 weeks after discontinuation; for *paroxysmal nocturnal haemoglobinuria*, monitor for intravascular haemolysis (including serum-lactate dehydrogenase concentration) during treatment and for at least 8 weeks after discontinuation

Meningococcal infection Vaccinate against *Neisseria meningitidis* at least 2 weeks before treatment (tetraavalent vaccine against serotypes A, C, W135 and Y recommended); revaccinate according to current medical guidelines. Patients receiving eculizumab less than 2 weeks after receiving meningococcal vaccine must be given prophylactic antibiotics until 2 weeks after vaccination. Advise child and carers to report promptly any signs of meningococcal infection. Other immunisations should also be up to date (section 14.1)

Contra-indications unresolved *Neisseria meningitidis* infection; patients unvaccinated against *Neisseria meningitidis* (see also Cautions above)

Pregnancy no information available—use only if potential benefit outweighs risk; human IgG antibodies known to cross placenta; manufacturer advises effective contraception during and for 5 months after treatment

Breast-feeding no information available—manufacturer advises avoid breast-feeding during and for 5 months after treatment

Side-effects gastro-intestinal disturbances; oedema; cough, nasopharyngitis; headache, dizziness, vertigo, fatigue, dysgeusia, paraesthesia; infection (including meningococcal infection); spontaneous erection, dysuria; arthralgia, myalgia; blood disorders (including thrombocytopenia, leucopenia); alopecia, pruritus, rash; influenza-like symptoms; infusion-related reactions; *less commonly* anorexia, gingival pain, jaundice, palpitation, haematoma, hypotension, chest pain, syncope, tremor, hot flushing, epistaxis, anxiety, depression, mood changes, sleep disturbances, Graves' disease, menstrual disorders, renal impairment, malignant melanoma, muscle spasms, myelodysplastic syndrome, visual disturbances, tinnitus, hyperhidrosis, petechiae, and skin depigmentation

Licensed use not licensed for use in children for paroxysmal nocturnal haemoglobinuria

Indications and dose

Atypical haemolytic uraemic syndrome (specialist use only)

- By intravenous infusion

Child 2 months–18 years

Body-weight 5–10 kg initially 300 mg once a week for 2 weeks, then 300 mg once every 3 weeks

Body-weight 10–20 kg initially 600 mg on week 1, then 300 mg on week 2, then 300 mg once every 2 weeks

Body-weight 20–30 kg initially 600 mg once a week for 3 weeks, then 600 mg once every 2 weeks

Body-weight 30–40 kg initially 600 mg once a week for 2 weeks, then 900 mg on week 3, then 900 mg once every 2 weeks

Body-weight over 40 kg initially 900 mg once a week for 4 weeks, then 1.2 g on week 5, then 1.2 g once every 2 weeks

Note Consult product literature for details of supplemental doses with concomitant plasmapheresis, plasma exchange, or plasma infusion

Paroxysmal nocturnal haemoglobinuria (specialist use only)

• **By intravenous infusion**

Refer for specialist advice, experience very limited

Administration dilute requisite dose to a concentration of 5 mg/mL with Glucose 5% or Sodium Chloride 0.9% and mix gently; give over 25–45 minutes; if infusion-related reactions occur, infusion time may be increased to 4 hours in child under 12 years or 2 hours in child over 12 years

Soliris[®] (Alexion) [PoM]

Concentrate for intravenous infusion, eculizumab 10 mg/mL, net price 30-mL vial = £3150.00. Counselling, meningococcal infection, patient information card

Electrolytes Na⁺ 5 mmol/vial

9.1.4 Drugs used in platelet disorders

Idiopathic thrombocytopenic purpura Acute idiopathic thrombocytopenic purpura is usually self-limiting in children. A **corticosteroid**, such as prednisolone (p. 382), is sometimes used if idiopathic thrombocytopenic purpura does not resolve spontaneously or if it is associated with severe cutaneous symptoms or mucous membrane bleeding; corticosteroid treatment should not be continued longer than 14 days regardless of the response.

Immunoglobulin preparations (section 14.5) may be used in idiopathic thrombocytopenic purpura or where a temporary rapid rise in platelets is needed, as in pregnancy or pre-operatively; they are often used in preference to a corticosteroid. Anti-D immunoglobulin is licensed for the management of idiopathic thrombocytopenic purpura.

Other therapy that has been tried under specialist supervision in refractory idiopathic thrombocytopenic purpura includes azathioprine (section 8.2.1), cyclophosphamide (section 8.1.1), vincristine (section 8.1.4), and cyclosporin (section 8.2.2). Rituximab is also used in specialist centres but experience of its use in children is limited. For patients with chronic severe thrombocytopenia refractory to other therapy, tranexamic acid (section 2.11) may be given to reduce the severity of haemorrhage.

Splenectomy is considered in chronic thrombocytopenic purpura if a satisfactory platelet count is not achieved with regular immunoglobulin infusions, if there is a relapse on withdrawing or reducing the dose of corticosteroid, and if other therapies are considered inappropriate.

Essential thrombocythaemia **Anagrelide** reduces platelets in essential thrombocythaemia in patients at risk of thrombo-haemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs.

ANAGRELIDE

Cautions cardiovascular disease—assess cardiac function before and during treatment; concomitant aspirin in patients at risk of haemorrhage; monitor full blood count (monitor platelet count every 2 days for 1 week, then weekly until maintenance dose estab-

lished), liver function, serum creatinine, and urea; **interactions:** Appendix 1 (anagrelide)

Skilled tasks Dizziness may affect performance of skilled tasks (e.g. driving)

Hepatic impairment manufacturer advises caution in mild impairment; avoid in moderate to severe impairment

Renal impairment manufacturer advises avoid if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid (toxicity in animal studies)

Breast-feeding manufacturer advises avoid—no information available

Side-effects gastro-intestinal disturbances, palpitation, tachycardia, fluid retention, headache, dizziness, fatigue, anaemia, rash; *less commonly* pancreatitis, gastro-intestinal haemorrhage, congestive heart failure, hypertension, arrhythmias, syncope, chest pain, dyspnoea, sleep disturbances, paraesthesia, hypoaesthesia, depression, nervousness, confusion, amnesia, fever, weight changes, impotence, blood disorders, myalgia, arthralgia, epistaxis, dry mouth, alopecia, skin discoloration, pruritus; *rarely* gastritis, colitis, postural hypotension, angina, myocardial infarction, vasodilatation, pulmonary hypertension, pulmonary infiltrates, migraine, drowsiness, impaired coordination, dysarthria, asthenia, tinnitus, renal failure, nocturia, visual disturbances, gingival bleeding; *also reported* allergic alveolitis, interstitial lung disease, pneumonitis, hepatitis, tubulointerstitial nephritis

Licensed use not licensed for use in children

Indications and dose

Essential thrombocythaemia in at-risk children who have not responded adequately to other therapy or who are intolerant of it (initiated under specialist supervision)

• **By mouth**

Child 7–18 years initially 500 micrograms daily adjusted according to response in steps of 500 micrograms daily at weekly intervals to max. 10 mg daily (max. single dose 2.5 mg); usual dose range 1–3 mg daily in divided doses

Xagrid[®] (Shire) ▼ [PoM]

Capsules, anagrelide (as hydrochloride), 500 micrograms, net price 100-cap pack = £404.57. Counselling, skilled tasks, see above

9.1.5 G6PD deficiency

Glucose 6-phosphate dehydrogenase (G6PD) deficiency is highly prevalent in individuals originating from most parts of Africa, from most parts of Asia, from Oceania, and from Southern Europe; it can also occur, rarely, in any other individuals. G6PD deficiency is more common in males than it is in females.

Individuals with G6PD deficiency are susceptible to developing acute haemolytic anaemia when they take a number of common drugs. They are also susceptible to developing acute haemolytic anaemia when they eat fava beans (broad beans, *Vicia faba*); this is termed *favism* and can be more severe in children or when the fresh fava beans are eaten raw.

When prescribing drugs for children with G6PD deficiency, the following three points should be kept in mind:

- G6PD deficiency is genetically heterogeneous; susceptibility to the haemolytic risk from drugs varies; thus, a drug found to be safe in some G6PD-deficient individuals may not be equally safe in others;
- manufacturers do not routinely test drugs for their effects in G6PD-deficient individuals;
- the risk and severity of haemolysis is almost always dose-related.

The lists below should be read with these points in mind. Ideally, information about G6PD deficiency should be available before prescribing a drug listed below. However, in the absence of this information, the possibility of haemolysis should be considered, especially if the child belongs to a group in which G6PD deficiency is common.

A very few G6PD-deficient individuals with chronic non-spherocytic haemolytic anaemia have haemolysis even in the absence of an exogenous trigger. These children must be regarded as being at high risk of severe exacerbation of haemolysis following administration of any of the drugs listed below.

Drugs with *definite* risk of haemolysis in most G6PD-deficient individuals

Dapsone and other sulfones (higher doses for dermatitis herpetiformis more likely to cause problems)

Methylthioninium chloride

Niridazole [not on UK market]

Nitrofurantoin

Pamaquin [not on UK market]

Primaquine (30 mg weekly for 8 weeks has been found to be without undue harmful effects in African and Asian people, see section 5.4.1)

Quinolones (including ciprofloxacin, moxifloxacin, nalidixic acid, norfloxacin, and ofloxacin)

Rasburicase

Sulfonamides (including co-trimoxazole; some sulfonamides, e.g. sulfadiazine, have been tested and found not to be haemolytic in many G6PD-deficient individuals)

Drugs with *possible* risk of haemolysis in some G6PD-deficient individuals

Aspirin (acceptable up to a dose of at least 1 g daily in most G6PD-deficient individuals)

Chloroquine (acceptable in acute malaria and malaria chemoprophylaxis)

Menadione, water-soluble derivatives (e.g. menadiol sodium phosphate)

Probenecid [not on UK market]

Quinidine (acceptable in acute malaria) [not on UK market]

Quinine (acceptable in acute malaria)

Sulfonylureas

Note Naphthalene in mothballs also causes haemolysis in individuals with G6PD-deficiency.

9.1.6 Drugs used in neutropenia

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) stimulates the production of neutrophils and may reduce the duration of chemotherapy-induced neutropenia and thereby reduce the incidence of associated sepsis; there is as yet no evidence that it improves overall survival. **Filgrastim** (unglycosylated rhG-CSF) and **lenograstim** (glycosylated rhG-CSF) have similar effects; both have been used in a variety of clinical settings, including cytotoxic-induced neutropenia, and neutropenia following bone marrow transplantation, but they do not have any clear-cut routine indications. In congenital neutropenia filgrastim usually increases the neutrophil count with an appropriate clinical response. Prolonged use may be associated with an increased risk of myeloid malignancy.

Treatment with granulocyte-colony stimulating factors should only be prescribed by those experienced in their use.

Neonatal neutropenia Filgrastim has been used to treat sepsis-induced neutropenia in preterm neonates. There is no clear evidence that granulocyte-colony stimulating factors improve survival or long-term outcomes.

Cautions Granulocyte-colony stimulating factors should be used with caution in patients with pre-malignant or malignant myeloid conditions. Full blood counts (including differential white cell count and platelet count) should be monitored. Treatment should be withdrawn in patients who develop signs of pulmonary infiltration. There have been reports of pulmonary infiltrates leading to acute respiratory distress syndrome—patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. Granulocyte-colony stimulating factors should be used with caution in children with sickle-cell disease. Spleen size should be monitored during treatment as there is a risk of splenomegaly and rupture.

Pregnancy There have been reports of toxicity in animal studies and manufacturers advise not to use granulocyte-colony stimulating factors during pregnancy unless the potential benefit outweighs the risk.

Breast-feeding There is no evidence for the use of granulocyte-colony stimulating factors during breast-feeding and manufacturers advise avoiding use.

Side-effects Side-effects of granulocyte-colony stimulating factors include gastro-intestinal disturbances, anorexia, headache, asthenia, fever, musculoskeletal pain, bone pain, rash, alopecia, injection-site reactions, thrombocytopenia, and leucocytosis. *Less commonly* chest pain can occur. Pulmonary side-effects, particularly interstitial pneumonia (see Cautions above), cutaneous vasculitis, and acute febrile neutrophilic dermatosis have *rarely* been reported.

FILGRASTIM

(Recombinant human granulocyte-colony stimulating factor, G-CSF)

Cautions see notes above; also regular morphological and cytogenetic bone-marrow examinations recommended in severe congenital neutropenia (possible risk of myelodysplastic syndromes or leukaemia); secondary acute myeloid leukaemia; osteoporotic

bone disease (monitor bone density if given for more than 6 months); **interactions:** Appendix 1 (filgrastim)

Contra-indications severe congenital neutropenia (Kostman's syndrome) with abnormal cytogenetics

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also mucositis, splenic enlargement, hepatomegaly, transient hypotension, epistaxis, urinary abnormalities (including dysuria, proteinuria, and haematuria), osteoporosis, exacerbation of rheumatoid arthritis, anaemia, transient decrease in blood glucose, pseudogout, and raised uric acid; *less commonly* capillary leak syndrome (including fatal cases); *very rarely* splenic rupture

Licensed use not reserved for treatment of glycogen storage disease or neonatal neutropenia

Indications and dose

Cytotoxic-induced neutropenia

- Preferably by subcutaneous injection or by intravenous infusion (over 30 minutes)

Child 1 month–18 years 5 micrograms/kg daily started not less than 24 hours after cytotoxic chemotherapy, continued until neutrophil count in normal range, usually for up to 14 days (up to 38 days in acute myeloid leukaemia)

Myeloablative therapy followed by bone-marrow transplantation

- By intravenous infusion over 30 minutes or over 24 hours or by subcutaneous injection over 24 hours

Child 1 month–18 years 10 micrograms/kg daily, started not less than 24 hours following cytotoxic chemotherapy (and within 24 hours of bone-marrow infusion), then adjusted according to absolute neutrophil count (consult product literature and local protocol)

Mobilisation of peripheral blood progenitor cells for autologous infusion, used alone

- By subcutaneous injection or by subcutaneous infusion over 24 hours

Child 1 month–18 years 10 micrograms/kg daily for 5–7 days

Mobilisation of peripheral blood progenitor cells for autologous infusion following adjunctive myelosuppressive chemotherapy (to improve yield)

- By subcutaneous injection

Child 1 month–18 years 5 micrograms/kg daily, started the day after completion of chemotherapy and continued until neutrophil count in normal range; for timing of leucopheresis consult product literature

Mobilisation of peripheral blood progenitor cells in normal donors for allogeneic infusion

- By subcutaneous injection

Child over 16 years 10 micrograms/kg daily for 4–5 days; for timing of leucopheresis consult product literature

Severe chronic neutropenia

- By subcutaneous injection

Child 1 month–18 years in severe congenital neutropenia, initially 12 micrograms/kg daily in single or divided doses (initially 5 micrograms/kg daily in idiopathic or cyclic neutropenia), adjusted according to response (consult product literature and local protocol)

Persistent neutropenia in HIV infection

- By subcutaneous injection

Child 1 month–18 years initially 1 microgram/kg daily, increased as necessary until absolute neutrophil count in normal range (usual max. 4 micrograms/kg daily), then adjusted to maintain absolute neutrophil count in normal range (consult product literature)

Neonatal neutropenia

- By subcutaneous injection

Neonate 10 micrograms/kg daily, discontinue if white cell count exceeds $50 \times 10^9/\text{litre}$

Glycogen storage disease type 1b

- By subcutaneous injection

5 micrograms/kg daily, adjusted as necessary

Administration For *subcutaneous* or *intravenous infusion*, dilute with Glucose 5% to a concentration of not less than 15 micrograms/mL; to dilute to a concentration of 2–15 micrograms/mL, add albumin solution (human albumin solution) to produce a final albumin solution of 2 mg/mL; not compatible with Sodium Chloride solutions

Neupogen® (Amgen) (PoM)

Injection, filgrastim 30 million units (300 micrograms)/mL; net price 1-mL vial = £52.70

Injection (Singleject®), filgrastim 60 million units (600 micrograms)/mL, net price 0.5-mL prefilled syringe = £52.70; 96 million units (960 micrograms)/mL, 0.5-mL prefilled syringe = £84.06

Nivestim® (Hospira) ▼ (PoM)

Injection, prefilled syringe, filgrastim, net price 12 million-units (120 micrograms)/0.2 mL = £36.00; 30 million-units (300 micrograms)/0.5 mL = £58.00; 48 million-units (480 micrograms)/0.5 mL = £93.00

Note Biosimilar medicine, p. 2

Ratiograstim® (Ratiopharm UK) ▼ (PoM)

Injection, prefilled syringe, filgrastim, net price 30 million-units (300 micrograms)/0.5 mL = £62.25; 48 million-units (480 micrograms)/0.8 mL = £99.29

Note Biosimilar medicine, p. 2

Zarzio® (Sandoz) (PoM)

Injection, prefilled syringe, filgrastim, net price 30 million-units (300 micrograms)/0.5 mL = £50.15; 48 million-units (480 micrograms)/0.5 mL = £79.90

Note Biosimilar medicine, p. 2

LENOGRASTIM

(Recombinant human granulocyte-colony stimulating factor, rHuG-CSF)

Cautions see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also splenic rupture and toxic epidermal necrolysis

Licensed use not licensed for use in children for cytotoxic-induced neutropenia, mobilisation of peripheral blood progenitor cells (monotherapy or adjunctive therapy), or following peripheral stem cells transplantation

Indications and dose

Following peripheral stem cells or bone-marrow transplantation

- By intravenous infusion over 30 minutes or by subcutaneous injection

Child 2–18 years 150 micrograms/m² daily started the day after transplantation, continued until neutrophil count stable in acceptable range (max. 28 days)

Cytotoxic-induced neutropenia

- By subcutaneous injection

Child 2–18 years 150 micrograms/m² daily started the day after completion of chemotherapy, continued until neutrophil count stable in acceptable range (max. 28 days)

Mobilisation of peripheral blood progenitor cells, used alone

- By subcutaneous injection

Child 2–18 years 10 micrograms/kg daily for 4–6 days (5–6 days in healthy donors)

Mobilisation of peripheral blood progenitor cells following adjunctive myelosuppressive chemotherapy (to improve yield)

- By subcutaneous injection

Child 2–18 years 150 micrograms/m² daily, started 1–5 days after completion of chemotherapy and continued until neutrophil count in acceptable range; for timing of leucopheresis consult product literature

Administration for intravenous infusion, dilute reconstituted solution to a concentration of not less than 2 micrograms/mL (*Granocyte-13*) or 2.5 micrograms/mL (*Granocyte-34*) with Sodium Chloride 0.9%

Granocyte® (Chugai) PoM

Injection, powder for reconstitution, lenograstim, net price 13.4 million-unit (105-microgram) vial = £40.11; 33.6 million-unit (263-microgram) vial = £62.54 (both with 1-mL prefilled syringe water for injections)

Excipients include phenylalanine (section 9.4.1)

9.2 Fluids and electrolytes

9.2.1 Oral preparations for fluid and electrolyte imbalance

9.2.2 Parenteral preparations for fluid and electrolyte imbalance

The following tables give a selection of useful electrolyte values:

Electrolyte concentrations—intravenous fluids

	Millimoles per litre					
	Intravenous infusion	Na ⁺	K ⁺	HCO ₃ ⁻	Cl ⁻	Ca ²⁺
<i>Normal plasma values</i>		142	4.5	26	103	2.5
Sodium Chloride 0.9%	150	—	—	150	—	—
Compound Sodium Lactate (Hartmann's)	131	5	29	111	2	—
Sodium Chloride 0.45% and Glucose 5%	75	—	—	75	—	—
Potassium Chloride 0.15% and Glucose 5%	—	20	—	20	—	—
Potassium Chloride 0.15% and Sodium Chloride 0.9%	150	20	—	170	—	—
Potassium Chloride 0.3% and Glucose 5%	—	40	—	40	—	—
Potassium Chloride 0.3% and Sodium Chloride 0.9%	150	40	—	190	—	—
<i>To correct metabolic acidosis</i>						
Sodium Bicarbonate 1.26%	150	—	150	—	—	—
Sodium Bicarbonate 8.4% for cardiac arrest	1000	—	1000	—	—	—
Sodium Lactate (m/6)	167	—	167	—	—	—

Electrolyte content—gastro-intestinal secretions

Type of fluid	Millimoles per litre					
	H ⁺	Na ⁺	K ⁺	HCO ₃ ⁻	Cl ⁻	
Gastric	40–60	20–80	5–20	—	100–150	
Biliary	—	120–140	5–15	30–50	80–120	
Pancreatic	—	120–140	5–15	70–110	40–80	
Small bowel	—	120–140	5–15	20–40	90–130	

Faeces, vomit, or aspiration should be saved and analysed where possible if abnormal losses are suspected; where this is impracticable the approximations above may be helpful in planning replacement therapy

9.2.1 Oral preparations for fluid and electrolyte imbalance

9.2.1.1 Oral potassium

9.2.1.2 Oral sodium and water

9.2.1.3 Oral bicarbonate

Sodium and potassium salts, which may be given by mouth to prevent deficiencies or to treat established deficiencies of mild or moderate degree, are discussed in this section. Oral preparations for removing excess potassium and preparations for oral rehydration therapy are also included here. Oral bicarbonate, for metabolic acidosis, is also described in this section.

For reference to calcium, magnesium, and phosphate, see section 9.5.

9.2.1.1 Oral potassium

Compensation for potassium loss is especially necessary:

- in children in whom secondary hyperaldosteronism occurs, e.g. renal artery stenosis, renal tubule disorder, the nephrotic syndrome, and severe heart failure;
- in children with excessive losses of potassium in the faeces, e.g. chronic diarrhoea associated with intestinal malabsorption or laxative abuse;
- in those taking digoxin or anti-arrhythmic drugs, where potassium depletion may induce arrhythmias.

Measures to compensate for potassium loss may be required during long-term administration of drugs known to induce potassium loss (e.g. corticosteroids). Potassium supplements are **seldom required** with the small doses of diuretics given to treat hypertension; **potassium-sparing diuretics** (rather than potassium supplements) are recommended for prevention of hypokalaemia due to diuretics such as furosemide or the thiazides when these are given to eliminate oedema.

Dosage If potassium salts are used for the *prevention of hypokalaemia*, then doses of potassium chloride 1–2 mmol/kg (usual max. 50 mmol potassium) daily by mouth are suitable in patients taking a normal diet. *Smaller doses* must be used if there is *renal insufficiency* to reduce the risk of **hyperkalaemia**. Potassium salts cause nausea and vomiting and poor compliance is a major limitation to their effectiveness (small divided doses may minimise gastric irritation); when appropriate, potassium-sparing diuretics are preferable (see also above). Regular monitoring of plasma-potassium concentration is essential in those taking potassium supplements. When there is *established potassium depletion* larger doses may be necessary, the quantity depending on the severity of any continuing potassium loss (monitoring of plasma-potassium concentration and specialist advice would be required). Potassium depletion is frequently associated with chloride depletion and with metabolic alkalosis, and these disorders require correction.

Administration Potassium salts are preferably given as a liquid (or effervescent) preparation, rather than modified-release tablets; they should be given as the chloride (the use of effervescent potassium tablets BPC 1968 should be restricted to *hyperchloraemic states*, section 9.2.1.3). Potassium chloride solutions suitable for use by mouth in neonates are available from 'special-order' manufacturers or specialist importing companies, see p. 840; they should be used with care because they are hypertonic and can damage the gastric mucosa.

Salt substitutes A number of salt substitutes which contain significant amounts of potassium chloride are readily available as health food products (e.g. *LoSalt*® and *Ruthmol*®). These should not be used by patients with renal failure as potassium intoxication may result.

POTASSIUM CHLORIDE

Cautions see notes above; cardiac disease; with *modified-release preparations*, intestinal stricture, history of peptic ulcer, hiatus hernia; **interactions:** Appendix 1 (potassium salts)

Contra-indications plasma-potassium concentration above 5 mmol/litre

Renal impairment close monitoring required—risk of hyperkalaemia; avoid in severe impairment

Side-effects nausea, vomiting, abdominal pain, diarrhoea, flatulence; with *modified-release preparations*, gastro-intestinal obstruction, ulceration, and bleeding also reported

Indications and dose

Potassium depletion

• By mouth

Neonate 0.5–1 mmol/kg K⁺ twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to plasma-potassium concentration

Child 1 month–18 years 0.5–1 mmol/kg K⁺ twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to plasma-potassium concentration

Note Do not confuse Effervescent Potassium Tablets BPC 1968 (section 9.2.1.3) with effervescent potassium chloride tablets. Effervescent Potassium Tablets BPC 1968 do not contain chloride ions and their use should be restricted to hyperchloraemic states (section 9.2.1.3).

Kay-Cee-L® (Geistlich)

Syrup, sugar-free, red, potassium chloride 7.5% (1 mmol/mL each of K⁺ and Cl⁻), net price 500 mL = £6.80. Label: 21

Sando-K® (HK Pharma)

Tablets, effervescent, potassium bicarbonate and chloride equivalent to potassium 470 mg (12 mmol of K⁺) and chloride 285 mg (8 mmol of Cl⁻), net price 20 = £1.53. Label: 13, 21

■ Modified-release preparations

Avoid unless effervescent tablets or liquid preparations inappropriate

Slow-K® (Alliance) 

Tablets, m/r, orange, s/c, potassium chloride 600 mg (8 mmol each of K⁺ and Cl⁻), net price 100 = £5.95. Label: 25, 27, counselling, swallow whole with fluid during meals while sitting or standing

Note May be difficult to obtain

Management of hyperkalaemia

Acute severe hyperkalaemia calls for urgent treatment with intravenous infusion of **soluble insulin** (0.3–0.6 units/kg/hour in neonates and 0.05–0.2 units/kg/hour in children over 1 month) with **glucose** 0.5–1 g/kg/hour (5–10 mL/kg of glucose 10%; 2.5–5 mL/kg of glucose 20% via a central venous catheter may also be considered). If insulin cannot be used, **salbutamol** (section 3.1.1.1) can be given by intravenous injection, but it has a slower onset of action and may be less effective for reducing plasma-potassium concentration.

Calcium gluconate (section 9.5.1.1) is given by slow intravenous injection to manage cardiac excitability caused by hyperkalaemia.

The correction of causal or compounding acidosis with **sodium bicarbonate** infusion (section 9.2.2.1) should be considered (**important:** preparations of sodium bicarbonate and calcium salts should not be administered in the same line—risk of precipitation). Intravenous **furosemide** can also be given but is less effective in children with renal impairment. Drugs exacerbating hyperkalaemia should be reviewed and stopped as appropriate; dialysis may occasionally be required.

Ion-exchange resins may be used to remove excess potassium in *mild hyperkalaemia* or in *moderate hyper-*

kalaemia when there are no ECG changes. Calcium polystyrene sulfonate is preferred unless plasma-calcium concentrations are high.

POLYSTYRENE SULFONATE RESINS

Cautions impaction of resin with excessive dosage or inadequate dilution; monitor for electrolyte disturbances (stop if plasma-potassium concentration below 5 mmol/litre); *sodium-containing resin* in congestive heart failure, hypertension, and oedema; **interactions:** Appendix 1 (polystyrene sulfonate resins)

Contra-indications obstructive bowel disease; neonates with reduced gut motility; *calcium-containing resin* in hyperparathyroidism, multiple myeloma, sarcoidosis, or metastatic carcinoma

Renal impairment use *sodium-containing resin* with caution

Pregnancy manufacturers advise use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturers advise use only if potential benefit outweighs risk—no information available

Side-effects faecal impaction following rectal administration, gastro-intestinal concretions following oral administration, intestinal necrosis reported with concomitant use of sorbitol, gastric irritation, anorexia, nausea, vomiting, constipation (discontinue treatment—avoid magnesium-containing laxatives), diarrhoea, hypomagnesaemia; gastro-intestinal obstruction, ulceration, necrosis, and ischaemic colitis also reported; with *calcium-containing resin*, hypercalcaemia (including in dialysed patients and occasionally those with renal impairment); with *sodium-containing resin*, sodium retention, hypocalcaemia

Indications and dose

See under preparations

Calcium Resonium® (Sanofi-Aventis)

Powder, buff, calcium polystyrene sulfonate, net price 300 g = £68.47. Label: 13

Dose

Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients

• By mouth

Child 1 month–18 years 0.5–1 g/kg (max. 60 g) daily in divided doses

Administration Administer in a small amount of water or honey—do not give with fruit juice or squash, which have a high potassium content

• By rectum

Neonate 0.5–1 g/kg daily. Irrigate colon to remove resin after 8–12 hours

Child 1 month–18 years 0.5–1 g/kg (max. 30 g) daily. Irrigate colon to remove resin after 8–12 hours

Administration Mix each 1 g of resin with 5 mL of water or 10% glucose

Resonium A® (Sanofi-Aventis)

Powder, buff, sodium polystyrene sulfonate, net price 454 g = £67.50. Label: 13

Dose

Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients

• By mouth

Child 1 month–18 years 0.5–1 g/kg (max. 60 g) daily in divided doses

Administration Administer in a small amount of water or honey—do not give with fruit juice or squash, which have a high potassium content

• By rectum

Neonate 0.5–1 g/kg daily. Irrigate colon to remove resin after 8–12 hours

Child 1 month–18 years 0.5–1 g/kg (max. 30 g) daily. Irrigate colon to remove resin after 8–12 hours

Administration Mix each 1 g of resin with 5 mL of water or 10% glucose

Sorbister® (Stanningley) (Pohl)

Powder, buff, calcium polystyrene sulfonate 759–949 mg/g, net price 500 g = £49.95. Label: 13, 21

Excipients include sucrose 51–241 mg per 1 g of powder

Dose

Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients

• By mouth

Child 1 month–18 years 0.5–1 g/kg (max. 60 g) daily in at least 3 divided doses

Administration Administer in a small amount of water or soft drink—do not give with fruit juice or squash, which have a high potassium content

• By rectum

Neonate 0.5–1 g/kg daily. Irrigate colon to remove resin after 6 hours

Child 1 month–18 years 0.5–1 g/kg (max. 40 g) daily. Irrigate colon to remove resin after 6 hours

Administration Mix each 1 g of resin with 4 mL of 5% glucose

9.2.1.2 Oral sodium and water

Sodium chloride is indicated in states of sodium depletion. In preterm neonates in the first few weeks of life and in chronic conditions associated with mild or moderate degrees of sodium depletion, e.g. in salt-losing bowel or renal disease, oral supplements of sodium chloride (section 9.2.1.3) may be sufficient. Sodium chloride solutions suitable for use by mouth in neonates are available from 'special-order' manufacturers or specialist importing companies, see p. 840; they should be used with care because they are hypertonic. Supplementation with sodium chloride may be required to replace losses in children with cystic fibrosis particularly in warm weather.

SODIUM CHLORIDE

Indications and dose

See also section 9.2.2

Sodium supplementation in neonates

• By mouth

Preterm neonate 2 mmol/100 mL of formula feed or 3–4 mmol/100 mL of breast milk, consult dietician

Sodium replacement

• By mouth

Child 1 month–18 years according to requirements, generally 1–2 mmol/kg daily in divided doses, higher doses may be needed in severe depletion

Chronic renal loss

• By mouth

Child 1 month–18 years 1–2 mmol/kg daily in divided doses, adjusted according to requirements

Slow Sodium® (HK Pharma)

Tablets, m/r, sodium chloride 600 mg (approx. 10 mmol each of Na^+ and Cl^-). Net price 100-tab pack = £6.05. Label: 25

Capsules available from 'special-order' manufacturers or specialist importing companies, see p. 840

Oral rehydration therapy (ORT)

Diarrhoea in children is usually self-limiting, however, in children under 6 months of age, and more particularly in those under 3 months, symptoms of dehydration may be less obvious and there is a risk of rapid and severe deterioration. Intestinal absorption of sodium and water is enhanced by glucose (and other carbohydrates). Replacement of fluid and electrolytes lost through diarrhoea can therefore be achieved by giving solutions containing sodium, potassium, and glucose or another carbohydrate such as rice starch.

Oral rehydration solutions should:

- enhance the absorption of water and electrolytes;
- replace the electrolyte deficit adequately and safely;
- contain an alkalising agent to counter acidosis;
- be slightly hypo-osmolar (about 250 mmol/litre) to prevent the possible induction of osmotic diarrhoea;
- be simple to use in hospital and at home;
- be palatable and acceptable, especially to children;
- be readily available.

It is the policy of the World Health Organization (WHO) to promote a single oral rehydration solution but to use it flexibly (e.g. by giving extra water between drinks of oral rehydration solution to moderately dehydrated infants).

Oral rehydration solutions used in the UK are lower in sodium (50–60 mmol/litre) than the WHO formulation since, in general, patients suffer less severe sodium loss.

Rehydration should be rapid over 3 to 4 hours (except in hypernatraemic dehydration in which case rehydration should occur more slowly over 12 hours). The patient should be reassessed after initial rehydration and if still dehydrated rapid fluid replacement should continue.

Once rehydration is complete further dehydration is prevented by encouraging the patient to drink normal volumes of an appropriate fluid and by replacing continuing losses with an oral rehydration solution; in infants, breast-feeding or formula feeds should be offered between oral rehydration drinks.

For intravenous rehydration see section 9.2.2.

ORAL REHYDRATION SALTS (ORS)

Licensed use *Dioralyte® Relief* not licensed for use in children under 3 months

Indications and dose

Fluid and electrolyte loss in diarrhoea see notes above

● **By mouth**

Child 1 month–1 year 1–1½ times usual feed volume

Child 1–12 years 200 mL after every loose motion

Child 12–18 years 200–400 mL after every loose motion

■ UK formulations

Note After reconstitution any unused solution should be discarded no later than 1 hour after preparation unless stored in a refrigerator when it may be kept for up to 24 hours.

Dioralyte® (Sanofi-Aventis)

Oral powder, sodium chloride 470 mg, potassium chloride 300 mg, disodium hydrogen citrate 530 mg, glucose 3.56 g/sachet, net price 6-sachet pack = £2.25, 20-sachet pack (black currant- or citrus-flavoured or natural) = £6.72

Note Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets reconstituted with 1 litre of water provide Na^+ 60 mmol, K^+ 20 mmol, Cl^- 60 mmol, citrate 10 mmol, and glucose 90 mmol

Dioralyte® Relief (Sanofi-Aventis)

Oral powder, sodium chloride 350 mg, potassium chloride 300 mg, sodium citrate 580 mg, cooked rice powder 6 g/sachet, net price 6-sachet pack (apricot-, black currant- or raspberry-flavoured) = £2.50, 20-sachet pack (apricot-flavoured) = £7.13

Note Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na^+ 60 mmol, K^+ 20 mmol, Cl^- 50 mmol and citrate 10 mmol; contains aspartame (section 9.4.1)

Electrolade® (Actavis)

Oral powder, sodium chloride 236 mg, potassium chloride 300 mg, sodium bicarbonate 500 mg, anhydrous glucose 4 g/sachet (banana-, black currant-, lemon and lime-, or orange-flavoured). Net price 6-sachet (plain or multiflavoured) pack = £1.33, 20-sachet (single- or multiflavoured) pack = £4.99

Note Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na^+ 50 mmol, K^+ 20 mmol, Cl^- 40 mmol, HCO_3^- 30 mmol, and glucose 111 mmol

■ WHO formulation**Oral Rehydration Salts** (Non-proprietary)

Oral powder, sodium chloride 2.6 g, potassium chloride 1.5 g, sodium citrate 2.9 g, anhydrous glucose 13.5 g. To be dissolved in sufficient water to produce 1 litre (providing Na^+ 75 mmol, K^+ 20 mmol, Cl^- 65 mmol, citrate 10 mmol, glucose 75 mmol/litre)

Note Recommended by the WHO and the United Nations Children's Fund but not commonly used in the UK

9.2.1.3 Oral bicarbonate

Sodium bicarbonate is given by mouth for *chronic acidotic states* such as uraemic acidosis or renal tubular acidosis. The dose for correction of metabolic acidosis is not predictable and the response must be assessed. For severe *metabolic acidosis*, sodium bicarbonate can be given intravenously (section 9.2.2).

Sodium supplements may increase blood pressure or cause fluid retention and pulmonary oedema in those at risk; hypokalaemia may be exacerbated.

Sodium bicarbonate may affect the stability or absorption of other drugs if administered at the same time. If possible, allow 1–2 hours before administering other drugs orally.

Where *hyperchloraemic acidosis* is associated with potassium deficiency, as in some renal tubular and gastrointestinal disorders it may be appropriate to give oral **potassium bicarbonate**, although acute or severe deficiency should be managed by intravenous therapy.

SODIUM BICARBONATE

Cautions see notes above; respiratory acidosis; interactions: Appendix 1 (antacids)

Indications and dose

Renal acidosis (see also notes above)

• By mouth

Neonate initially 1–2 mmol/kg daily in divided doses, adjusted according to response

Child 1 month–18 years initially 1–2 mmol/kg daily in divided doses, adjusted according to response

Metabolic acidosis section 9.2.2.1

Renal hyperkalaemia section 9.2.2.1

Sodium Bicarbonate (Non-proprietary)

Capsules, sodium bicarbonate 500 mg (approx. 6 mmol each of Na^+ and HCO_3^-), net price 56-cap pack = £2.66

Tablets, sodium bicarbonate 600 mg, net price 100-tab pack = £27.14

Important Oral solutions of sodium bicarbonate are required occasionally; these need to be obtained from 'special-order' manufacturers or specialist importing companies, see p. 840, and the strength of sodium bicarbonate should be stated on the prescription

POTASSIUM BICARBONATE

Cautions cardiac disease, interactions: Appendix 1 (potassium salts)

Contra-indications hypochloraemia; plasma-potassium concentration above 5 mmol/litre

Renal impairment close monitoring required—high risk of hyperkalaemia; avoid in severe impairment

Side-effects nausea, vomiting, abdominal pain, diarrhoea, and flatulence

Potassium Tablets, Effervescent (Non-proprietary)

Effervescent tablets, potassium bicarbonate 500 mg, potassium acid tartrate 300 mg, each tablet providing 6.5 mmol of K^+ . To be dissolved in water before administration. Net price 56 = £87.25. Label: 13, 21

Note These tablets do not contain chloride; for effervescent tablets containing potassium and chloride, see under Potassium Chloride, section 9.2.1.1

9.2.2 Parenteral preparations for fluid and electrolyte imbalance

9.2.2.1 Electrolytes and water

9.2.2.2 Plasma and plasma substitutes

9.2.2.1 Electrolytes and water

Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses when it is not possible or desirable to use the oral route. When intravenous administration is not possible, fluid (as sodium chloride 0.9% or glucose 5%) can also be given subcutaneously by hypodermoclysis.

In an individual patient the nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical examination. Sodium,

potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acid-base balance; for reference to the use of magnesium and phosphates, see section 9.5.

Isotonic solutions may be infused safely into a peripheral vein. Solutions more concentrated than plasma, for example 15% glucose, are best given through an indwelling catheter positioned in a large vein.

Maintenance fluid requirements in children are usually derived from the relationship that exists between body-weight and metabolic rate; the figures in the table below may be used as a guide outside the neonatal period. The glucose requirement is that needed to minimise gluconeogenesis from amino acids obtained as substrate from muscle breakdown. Maintenance fluids are intended only to provide hydration for a short period until enteral or parenteral nutrition can be established.

It is usual to meet these requirements by using a standard solution of sodium chloride and glucose. Solutions containing 20 mmol/litre of potassium chloride meet usual potassium requirements when given in the suggested volumes; adjustments may be needed if there is an inability to excrete fluids or electrolytes, excessive renal loss or continuing extra-renal losses. The exact requirements depend upon the nature of the clinical situation and types of losses incurred; see Caution on dilutional hyponatraemia below.

Fluid requirements for children over 1 month:

Body-weight	24-hour fluid requirement
Under 10 kg	100 mL/kg
10–20 kg	100 mL/kg for the first 10 kg + 50 mL/kg for each 1 kg body-weight over 10 kg
Over 20 kg	100 mL/kg for the first 10 kg + 50 mL/kg for each 1 kg body-weight between 10–20 kg + 20 mL/kg for each 1 kg body-weight over 20 kg (max. 2 litres in females, 2.5 litres in males)

Important The baseline fluid requirements shown in the table above should be adjusted to take account of factors that reduce water loss (e.g. increased antidiuretic hormone, renal failure, hypothermia, and high ambient humidity) or increase water loss (e.g. pyrexia or burns).

Caution During parenteral hydration, fluids and electrolytes should be monitored closely and any disturbance corrected by slow infusion of an appropriate solution. The volume of fluid infused should take into account the possibility of reduced fluid loss owing to increased antidiuretic hormone and factors such as renal failure, hypothermia, and high humidity.

Dilutional hyponatraemia is a rare but potentially fatal risk of parenteral hydration. It may be caused by inappropriate use of hypotonic fluids such as sodium chloride 0.18% and glucose 4% intravenous infusion, especially in the postoperative period when antidiuretic hormone secretion is increased. Dilutional hyponatr-

aemia is characterized by a rapid fall in plasma-sodium concentration leading to cerebral oedema and seizures; any child with severe hyponatraemia or rapidly changing plasma-sodium concentration should be referred urgently to a paediatric high dependency facility.

Safe practice

Sodium chloride 0.18% and glucose 4% intravenous infusion fluid should not be used for fluid replacement in children aged 16 years or less because of the risk of hyponatraemia; availability of this infusion should be restricted to high dependency and intensive care units, and specialist wards, such as renal, liver, and cardiac units. Local guidelines on intravenous fluids should be consulted.

Replacement therapy: initial intravenous replacement fluid is generally required if the child is over 10% dehydrated, or if 5–10% dehydrated and oral or enteral rehydration is not tolerated or possible. Oral rehydration is adequate, if tolerated, in the majority of those less than 10% dehydrated. Subsequent fluid and electrolyte requirements are determined by clinical assessment of fluid balance.

Neonates Neonates lose water through the skin and nose, particularly if preterm or if the skin is damaged. The basic fluid requirement for a term baby in average ambient humidity is 40–60 mL/kg/day plus urinary losses. Preterm babies have very high transepidermal losses particularly in the first few days of life; they may need more fluid replacement than full term babies and up to 180 mL/kg/day may be required. Local guidelines for fluid management in the neonatal period should be consulted.

Intravenous sodium

Intravenous sodium chloride in isotonic (0.9%) solution provides the most important extracellular ions in near physiological concentrations and is indicated in *sodium depletion*. It may be given for initial treatment of acute fluid loss and to replace ongoing gastro-intestinal losses from the upper gastro-intestinal tract. Intravenous sodium chloride is commonly given as a component of maintenance and replacement therapy, usually in combination with other electrolytes and glucose, see notes above. Sodium chloride solutions should be used cautiously in renal insufficiency, cardiac failure, cardio-respiratory diseases, hepatic cirrhosis and in children receiving glucocorticoids. Hyponatraemia with serious consequences may occur if maintenance and replacement fluids do not meet sodium requirements (see Caution, dilutional hyponatraemia, above).

Chronic hyponatraemia should ideally be corrected by fluid restriction. However, if sodium chloride is required, the deficit should be corrected slowly to avoid the risk of osmotic demyelination syndrome; the rise in plasma-sodium concentration should be no more than 10 mmol/litre in 24 hours.

Sodium chloride and glucose solutions are indicated when there is combined *water and sodium depletion*. A 1:1 mixture of isotonic sodium chloride and 5% glucose allows some of the water (free of sodium) to enter body cells which suffer most from dehydration while the sodium salt with a volume of water determined by the normal plasma Na^+ remains extracellular. Maintenance fluid should accurately reflect daily requirements and close monitoring is required to avoid fluid and electro-

lyte imbalance. Illness or injury increase the secretion of anti-diuretic hormone and therefore the ability to excrete excess water may be impaired. Inappropriate use of hypotonic solutions such as sodium chloride 0.18% and glucose 4% may also cause dilutional hyponatraemia especially in children (see Caution on dilutional hyponatraemia, above); if necessary, guidance should be sought from a clinician experienced in the management of fluid and electrolytes.

Combined sodium, potassium, chloride, and water depletion may occur, for example, with severe diarrhoea or persistent vomiting; replacement is carried out with sodium chloride intravenous infusion 0.9% and glucose intravenous infusion 5% with potassium as appropriate.

Compound sodium lactate (Hartmann's solution) can be used instead of isotonic sodium chloride solution during or after surgery, or in the initial management of the injured or wounded.

Neonates The sodium requirement for most healthy neonates is 3 mmol/kg daily. Preterm neonates, particularly below 30 weeks gestation, may require up to 6 mmol/kg daily. *Hyponatraemia* may be caused by excessive renal loss of sodium; it may also be dilutional and restriction of fluid intake may be appropriate. Sodium supplementation is likely to be required if the serum sodium concentration is significantly reduced.

Hypernatraemia may also occur, most often due to dehydration (e.g. breast milk insufficiency). Severe hypernatraemia and hyponatraemia can cause fits and rarely brain damage. Sodium in drug preparations, delivered via continuous infusions, or in infusions to maintain the patency of intravascular or umbilical lines, can result in significant amounts of sodium being delivered, (e.g. 1 mL/hour of 0.9% sodium chloride infused over 24 hours is equivalent to 3.6 mmol/day of sodium).

SODIUM CHLORIDE

Cautions restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, toxemia of pregnancy; see also notes above

Side-effects administration of large doses may give rise to sodium accumulation and oedema

Indications and dose

Electrolyte imbalance see notes above, also section 9.2.1.2

Sodium Chloride (Non-proprietary) [PoM]

Intravenous infusion, usual strength sodium chloride 0.9% (9 g, 150 mmol each of Na^+ and Cl^- /litre), this strength being supplied when normal saline for injection is requested. Net price 2-mL amp = 21p; 5-mL amp = 28p; 10-mL amp = 34p; 20-mL amp = £1.04; 50-mL amp = £3.63

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

Note The term 'normal saline' should not be used to describe sodium chloride intravenous infusion 0.9%; the term 'physiological saline' is acceptable but it is preferable to give the composition (i.e. sodium chloride intravenous infusion 0.9%).

With other ingredients

Note See above for warning on hyponatraemia

Sodium Chloride and Glucose (Non-proprietary) [PoM]

Intravenous infusion, sodium chloride 0.18% (Na^+ and Cl^- each 30 mmol/litre), glucose 4%

In hospitals, usually 500-mL packs and sometimes other sizes are available

Intravenous infusion, sodium chloride 0.45% (Na⁺ and Cl⁻ each 75 mmol/litre), glucose 5%

In hospitals, usually 500-mL packs and sometimes other sizes are available

Intravenous infusion, sodium chloride 0.9% (Na⁺ and Cl⁻ each 150 mmol/litre), glucose 5%

In hospitals, usually 500-mL packs and sometimes other sizes are available

Ringer's Solution (Non-proprietary) (PoM)

Calcium chloride (dihydrate) 322 micrograms, potassium chloride 300 micrograms, sodium chloride 8.6 mg/mL, providing the following ions (in mmol/litre), Ca²⁺ 2.2, K⁺ 4, Na⁺ 147, Cl⁻ 156

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

Sodium Lactate, Compound (Non-proprietary) (PoM) (Hartmann's Solution; Ringer-Lactate Solution)

Intravenous infusion, sodium chloride 0.6%, sodium lactate 0.32%, potassium chloride 0.04%, calcium chloride 0.027% (containing Na⁺ 131 mmol, K⁺ 5 mmol, Ca²⁺ 2 mmol, HCO₃⁻ (as lactate) 29 mmol, Cl⁻ 111 mmol/litre)

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

Intravenous glucose

Glucose solutions are used mainly to replace water deficit and should not be given alone except when there is no significant loss of electrolytes; prolonged administration of glucose solutions without electrolytes can lead to hyponatraemia and other electrolyte disturbances. Water depletion (dehydration) tends to occur when losses are not matched by a comparable intake, as may occur in coma or dysphagia.

Water loss rarely exceeds electrolyte losses but this can occur in fevers, hyperthyroidism, and in uncommon water-losing renal states such as diabetes insipidus or hypercalcaemia. The volume of glucose solution needed to replace deficits varies with the severity of the disorder; the rate of infusion should be adjusted to return the plasma-sodium concentration to normal over 48 hours.

Glucose solutions are also used to correct and prevent hypoglycaemia and to provide a source of energy in those too ill to be fed adequately by mouth; glucose solutions are a key component of parenteral nutrition (section 9.3).

Glucose solutions are given with insulin for the emergency management of *hyperkalaemia* (see p. 464). They are also given, after correction of hyperglycaemia, during treatment of diabetic ketoacidosis, when they must be accompanied by continuous insulin infusion (section 6.1.3).

Injections containing more than 10% glucose can be irritant and should be given into a central venous line; however, solutions containing up to 12.5% can be administered for a short period into a peripheral line.

GLUCOSE

(Dextrose Monohydrate)

Note Glucose BP is the monohydrate but Glucose Intravenous Infusion BP is a sterile solution of anhydrous glucose or glucose monohydrate, potency being expressed in terms of anhydrous glucose

Side-effects glucose injections especially if hypertonic may have a low pH and may cause venous irritation and thrombophlebitis

Indications and dose

Fluid replacement see notes above

Provision of energy section 9.3

Hypoglycaemia section 6.1.4

Glucose (Non-proprietary) (PoM)

Intravenous infusion, glucose or anhydrous glucose (potency expressed in terms of anhydrous glucose), usual strengths 5% (50 mg/mL), 10% (100 mg/mL), and 20% (200 mg/mL); 20% solution, net price 20-mL amp = £2.04; 50% solution¹, 20-mL amp = £1.00, 50-mL vial = £2.02

In hospitals, 500- and 1000-mL packs, and sometimes other sizes and strengths, are available; also available *Minijet*[®] Glucose, 50% in 50-mL disposable syringe¹

Intravenous potassium

Potassium chloride and sodium chloride intravenous infusion is the initial treatment for the correction of *severe hypokalaemia* and when sufficient potassium cannot be taken by mouth. Ready-mixed infusion solutions should be used when possible (see under Safe Practice below); for peripheral intravenous infusion, the concentration of potassium should not usually exceed 40 mmol/litre. Potassium infusions should be given slowly over at least 2–3 hours and at a rate not exceeding 0.2 mmol/kg/hour with specialist advice and ECG monitoring in difficult cases. Higher concentrations of potassium chloride or faster infusion rates may be given in very severe depletion, but require specialist advice.

Repeated measurements of plasma-potassium concentration are necessary to determine whether further infusions are required and to avoid the development of hyperkalaemia, which is especially likely in renal impairment.

Initial potassium replacement therapy should **not** involve glucose infusions, because glucose may cause a further decrease in the plasma-potassium concentration.

Safe Practice

Potassium overdose can be fatal. Ready-mixed infusion solutions containing potassium should be used. Exceptionally, if potassium chloride concentrate is used for preparing an infusion, the infusion solution should be **thoroughly mixed**. Local policies on avoiding inadvertent use of potassium chloride concentrate should be followed.

POTASSIUM CHLORIDE

Cautions for peripheral intravenous infusion the concentration of solution should not usually exceed 3 g (40 mmol)/litre; specialist advice and ECG monitoring (see notes above); **interactions:** Appendix 1 (potassium salts)

Contra-indications plasma-potassium concentration above 5 mmol/litre

Renal impairment close monitoring required—high risk of hyperkalaemia; avoid in severe impairment

Side-effects rapid infusion toxic to heart

1. (PoM) restriction does not apply where administration is for saving life in emergency

Indications and dose

Electrolyte imbalance see also oral potassium supplements, section 9.2.1.1

- **By slow intravenous infusion**

Depending on the deficit or the daily maintenance requirements, see also notes above

Neonate 1–2 mmol/kg daily

Child 1 month–18 years 1–2 mmol/kg daily

Administration see notes above

Potassium Chloride and Glucose (Non-

proprietary) (PoM)

Intravenous infusion, usual strengths potassium chloride 0.3% (3 g, 40 mmol each of K^+ and Cl^- /litre) or 0.15% (1.5 g, 20 mmol each of K^+ and Cl^- /litre) with 5% of anhydrous glucose

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

Potassium Chloride and Sodium Chloride (Non-

proprietary) (PoM)

Intravenous infusion, usual strength potassium chloride 0.15% (1.5 g/litre) with sodium chloride 0.9% (9 g/litre), containing K^+ 20 mmol, Na^+ 150 mmol, and Cl^- 170 mmol/litre

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

Potassium Chloride, Sodium Chloride, and

Glucose (Non-proprietary) (PoM)

Intravenous infusion, sodium chloride 0.45% (4.5 g, Na^+ 75 mmol/litre) with 5% of anhydrous glucose and usually sufficient potassium chloride to provide K^+ 10–40 mmol/litre (to be specified by the prescriber)

In hospitals, 500- and 1000-mL packs, and sometimes other sizes are available

Potassium Chloride (Non-proprietary) (PoM)

Sterile concentrate, potassium chloride 15%

(150 mg, approximately 2 mmol each of K^+ and Cl^- /mL). Net price 10-mL amp = 48p

Solutions containing 10 and 20% of potassium chloride are also available in both 5- and 10-mL ampoules

Important Must be diluted with **not less** than 50 times its volume of Sodium Chloride 0.9% or other suitable diluent and **mixed well**; see Safe Practice, above

Bicarbonate and trometamol

Sodium bicarbonate is used to control severe *metabolic acidosis* ($pH < 7.1$) particularly that caused by loss of bicarbonate (as in renal tubular acidosis or from excessive gastro-intestinal losses). Mild metabolic acidosis associated with volume depletion should first be managed by appropriate fluid replacement because acidosis usually resolves as tissue and renal perfusion are restored. In more severe metabolic acidosis or when the acidosis remains unresponsive to correction of anaemia or hypovolaemia, sodium bicarbonate (1.26%) can be infused over 3–4 hours with plasma-pH and electrolyte monitoring. In severe shock (section 2.7.1), for example in cardiac arrest, metabolic acidosis can develop without sodium depletion; in these circumstances sodium bicarbonate is best given intravenously as a small volume of hypertonic solution, such as 8.4%; plasma pH and electrolytes should be monitored. For *chronic acidotic states*, sodium bicarbonate can be given by mouth (section 9.2.1.3).

Trometamol (tris(hydroxymethyl)aminomethane, THAM), an organic buffer, corrects metabolic acidosis

by causing an increase in urinary pH and an osmotic diuresis. It is indicated when sodium bicarbonate is unsuitable as in carbon dioxide retention, hypernatraemia, or renal impairment. Respiratory support may be required because trometamol induces respiratory depression. It is also used during cardiac bypass surgery and, very rarely, in cardiac arrest.

SODIUM BICARBONATE**Indications and dose**

Metabolic acidosis see also notes above

- **By slow intravenous injection of a strong solution (up to 8.4%), or by continuous intravenous infusion of a weaker solution (usually 1.26%)**

An amount appropriate to the body base deficit

Renal hyperkalaemia

- **By slow intravenous injection**

Neonate 1 mmol/kg daily

Child 1 month–18 years 1 mmol/kg daily

Renal acidosis section 9.2.1.3

Sodium Bicarbonate (PoM)

Intravenous infusion, usual strength sodium bicarbonate 1.26% (12.6 g, 150 mmol each of Na^+ and HCO_3^- /litre); various other strengths available

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

Administration For *peripheral infusion* dilute 8.4% solution at least 1 in 10; for *central line infusion* dilute 1 in 5 with Glucose 5% or 10% or Sodium Chloride 0.9%. Extravasation can cause severe tissue damage

Minijet® Sodium Bicarbonate (UCB Pharma) (PoM)

Intravenous injection, sodium bicarbonate in disposable syringe, net price 4.2%, 10 mL = £11.03; 8.4%, 10 mL = £11.10, 50 mL = £12.15

TROMETAMOL

(Tris(hydroxymethyl)aminomethane, THAM)

Cautions see notes above; extravasation can cause severe tissue damage

Contra-indications anuria; chronic respiratory acidosis

Renal impairment use with caution, may cause hyperkalaemia

Pregnancy limited information available, hypoglycaemia may harm fetus

Breast-feeding no information available

Side-effects respiratory depression; hypoglycaemia; hyperkalaemia in renal impairment; liver necrosis reported following administration via umbilical vein in neonates

Licensed use unlicensed preparation

Indications and dose

Metabolic acidosis

- **By intravenous infusion**

An amount appropriate to the body base deficit

Preparations

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Water

Water for Injections (PoM)

Net price 1-mL amp = £0.18; 2-mL amp = £0.13; 5-mL amp = £0.24; 10-mL amp = £0.25, 10-mL vial = £1.40; 20-mL amp = £0.39; 50-mL amp = £1.91; 100-mL vial = £2.60

Note Water for Injections can be sold or supplied by a pharmacist for a purpose other than parenteral administration, or when dry powder for parenteral administration has been prescribed without the Water for Injections that is needed as a diluent

9.2.2.2 Plasma and plasma substitutes

Albumin solutions, prepared from whole blood, contain soluble proteins and electrolytes but no clotting factors, blood group antibodies, or plasma cholinesterases; they may be given without regard to the recipient's blood group.

Albumin is usually used after the acute phase of illness to correct a plasma-volume deficit; hypoalbuminaemia itself is not an appropriate indication. The use of albumin solutions in acute plasma or blood loss may be wasteful; plasma substitutes are more appropriate. Concentrated albumin solutions may also be used to obtain a diuresis in hypoalbuminaemic patients (e.g. in nephrotic syndrome).

Recent evidence does not support the previous view that the use of albumin increases mortality.

Plasma and plasma substitutes are often used in very ill children whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the child's condition at all times.

ALBUMIN SOLUTION (Human Albumin Solution)

A solution containing protein derived from plasma, serum, or normal placentas; at least 95% of the protein is albumin. The solution may be isotonic (containing 3.5–5% protein) or concentrated (containing 15–25% protein).

Cautions history of cardiac or circulatory disease (administer slowly to avoid rapid rise in blood pressure and cardiac failure, and monitor cardiovascular and respiratory function); increased capillary permeability; correct dehydration when administering concentrated solution

Contra-indications cardiac failure; severe anaemia

Side-effects hypersensitivity reactions (including anaphylaxis) with nausea, vomiting, increased salivation, fever, tachycardia, hypotension and chills reported

Indications and dose

See notes above and under preparations, below

Isotonic solutions

Indications: acute or sub-acute loss of plasma volume e.g. in burns, pancreatitis, trauma, and complications of surgery; plasma exchange

Available as: *Human Albumin Solution 4.5%* (50-, 100-, 250- and 400-mL bottles—Baxter); *Human Albumin Solution 5%* (250- and 500-mL bottles—Baxter); *Albumorm*® 5% (100-, 250-, and 500-mL bottles—Octapharma); *Zenalb*® 4.5% (50-, 100-, 250-, and 500-mL bottles—BPL)

Concentrated solutions (20%)

Indications: severe hypoalbuminaemia associated with low plasma volume and generalised oedema where salt and water restriction with plasma volume expansion are required; adjunct in the treatment of hyperbilirubinaemia by exchange transfusion in the newborn; paracentesis of large volume ascites associated with portal hypertension

Available as: *Human Albumin Solution 20%* (50- and 100-mL vials—Baxter); *Albumorm*® 20% (50- and 100-mL bottles—Octapharma); *Flexbumin*® 20% (50- and 100-mL bags—Baxter); *Zenalb*® 20% (50- and 100-mL bottles—BPL)

Plasma substitutes

Gelatin and the **etherified starch**, **pentastarch**, are macromolecular substances which are metabolised slowly; they may be used at the outset to expand and maintain blood volume in shock arising from conditions such as burns or septicaemia. Plasma substitutes may be used as an immediate short-term measure to treat haemorrhage until blood is available. They are rarely needed when shock is due to sodium and water depletion because, in these circumstances, the shock responds to water and electrolyte repletion; see also section 2.7.1 for the management of shock.

MHRA/CHM advice

MHRA suspends use of hydroxyethyl starch (HES) infusions (June 2013)

The use of hydroxyethyl starch infusions to treat critically ill patients and those undergoing surgery has been suspended in the UK because their benefits no longer outweigh the risk of using them. Studies have suggested an increased risk of renal injury and death in patients treated with these products compared with crystalloids (simple salt solutions).

Tetraspan®, *Venofundin*®, *Volulyte*®, and *Voluven*® have all been withdrawn by the manufacturers.

Plasma substitutes should **not** be used to maintain plasma volume in conditions such as burns or peritonitis where there is loss of plasma protein, water, and electrolytes over periods of several days or weeks. In these situations, plasma or plasma protein fractions containing large amounts of albumin should be given.

Large volumes of *some* plasma substitutes can increase the risk of bleeding through depletion of coagulation factors.

Plasma and plasma substitutes are often used in very ill children whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the child's condition at all times.

The use of plasma substitutes in children requires specialist supervision due to the risk of fluid overload; use is best restricted to an intensive care setting.

Cautions Plasma substitutes should be used with caution in cardiac disease, liver disease, or renal impairment; urine output should be monitored. Care should be taken to avoid haematocrit concentration from falling below 25–30% and the child should be monitored for hypersensitivity reactions.

Side-effects Hypersensitivity reactions may occur including, rarely, severe anaphylactic reactions. Transient increase in bleeding time may occur.

GELATIN

Note The gelatin is partially degraded

Cautions see notes above

Pregnancy manufacturer of *Geloplasma*® advises avoid at the end of pregnancy

Side-effects see notes above

Indications and dose

Low blood volume in hypovolaemic shock, burns and cardiopulmonary bypass

• By intravenous infusion

Initially 10–20 mL/kg of a 3.5–4% solution (see notes above)

Gelofusine® (B. Braun) (PoM)

Intravenous infusion, succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 154 mmol, Cl⁻ 124 mmol/litre, net price 500-mL *Ecobag*® = £4.83; 1-litre *Ecobag*® = £9.04
Contains traces of calcium

Geloplasma® (Fresenius Kabi) (PoM)

Intravenous infusion, partially hydrolysed and succinylated gelatin (modified liquid gelatin) (as anhydrous gelatin) 30 g (3%), Na⁺ 150 mmol, K⁺ 5 mmol, Mg²⁺ 1.5 mmol, Cl⁻ 100 mmol, lactate 30 mmol/litre, net price 500-mL bag = £5.05

Isoplex® (Beacon) (PoM)

Intravenous infusion, succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 145 mmol, K⁺ 4 mmol, Mg²⁺ 0.9 mmol, Cl⁻ 105 mmol, lactate 25 mmol/litre, net price 500-mL bag = £7.53; 1-litre bag = £14.54

Volplex® (Beacon) (PoM)

Intravenous infusion, succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 154 mmol, Cl⁻ 125 mmol/litre, net price 500-mL bag = £4.70; 1-litre bag = £9.09

ETHERIFIED STARCH

A starch composed of more than 90% of amylopectin that has been etherified with hydroxyethyl groups; the term pentastarch reflects the degree of etherification

Cautions see notes above

Renal impairment use with caution in mild to moderate impairment; avoid in severe impairment

Side-effects see notes above; also pruritus, raised serum amylase

Indications and dose

Low blood volume

• By intravenous infusion

According to the child's condition (see notes above)

■ Pentastarch

HAES-steril® (Fresenius Kabi) (PoM)

Intravenous infusion, pentastarch (weight average molecular weight 200 000) 10% in sodium chloride intravenous infusion 0.9%, net price, 500 mL = £16.50

Hemohe® (B. Braun) (PoM)

Intravenous infusion, pentastarch (weight average molecular weight 200 000), net price (both in sodium chloride intravenous infusion 0.9%) 6%, 500 mL = £12.50; 10%, 500 mL = £16.50

9.3 Intravenous nutrition

When adequate feeding through the alimentary tract is not possible, nutrients may be given by intravenous infusion. This may be in addition to oral or enteral tube feeding—**supplemental parenteral nutrition**, or may be the sole source of nutrition—**total parenteral nutrition** (TPN). Complete enteral starvation is undesirable and total parenteral nutrition is a last resort.

Indications for parenteral nutrition include prematurity; severe or prolonged disorders of the gastro-intestinal tract; preparation of undernourished patients for surgery, chemotherapy, or radiation therapy; major surgery, trauma, or burns; prolonged coma or inability to eat; and some patients with renal or hepatic failure. The composition of proprietary preparations used in children is given under Proprietary Infusion Fluids for Parenteral Feeding, p. 473

Parenteral nutrition requires the use of a solution containing amino acids, glucose, lipids, electrolytes, trace elements, and vitamins. This is now commonly provided by the pharmacy in the form of an amino-acid, glucose, electrolyte bag, and a separate lipid infusion or, in older children a single 'all-in-one' bag. If the patient is able to take small amounts by mouth, vitamins may be given orally.

The nutrition solution is infused through a central venous catheter inserted under full surgical precautions. Alternatively, infusion through a peripheral vein may be used for supplementary as well as total parenteral nutrition, depending on the availability of peripheral veins; factors prolonging cannula life and preventing thrombophlebitis include the use of soft polyurethane paediatric cannulas and use of nutritional solutions of low osmolality and neutral pH. Nutritional fluids should be given by a dedicated intravenous line; if not possible, compatibility with any drugs or fluids should be checked as precipitation of components may occur. Extravasation of parenteral nutrition solution can cause severe tissue damage and injury; the infusion site should be regularly monitored.

Before starting intravenous nutrition the patient should be clinically stable and renal function and acid-base status should be assessed. Appropriate biochemical tests should have been carried out beforehand and serious deficits corrected. Nutritional and electrolyte status must be monitored throughout treatment. The nutritional components of parenteral nutrition regimens are usually increased gradually over a number of days to prevent metabolic complications and to allow metabolic adaptation to the infused nutrients. The solutions are usually infused over 24 hours but this may be gradually reduced if long-term nutrition is required. Home parenteral nutrition is usually infused over 12 hours overnight.

Complications of long-term parenteral nutrition include gall bladder sludging, gall stones, cholestasis and abnormal liver function tests. For details of the prevention and management of parenteral nutrition complications, specialist literature should be consulted.

Proprietary Infusion Fluids for Parenteral Feeding

Preparation	Nitrogen g/litre	^{1,2} Energy kJ/litre	Electrolytes mmol/litre					Other components/litre
			K ⁺	Mg ²⁺	Na ⁺	Acet ⁻	Cl ⁻	
ClinOleic 20% (Baxter) Net price 100 mL = £6.28; 250 mL = £10.08; 500 mL = £13.88	—	8360	—	—	—	—	—	purified olive and soya oil 200 g, glycerol 22.5 g, egg phosphatides 12 g
Glamin (Fresenius Kabi) Net price 250 mL = £14.58; 500 mL = £27.20	22.4	—	—	—	—	62	—	—
Intralipid 10% (Fresenius Kabi) Net price 100 mL = £4.85; 500 mL = £10.60	—	4600	—	—	—	—	—	soya oil 100 g, glycerol 22 g, purified egg phospholipids 12 g, phosphate 15 mmol
Intralipid 20% (Fresenius Kabi) Net price 100 mL = £7.30; 250 mL = £11.95; 500 mL = £15.90	—	8400	—	—	—	—	—	soya oil 200 g, glycerol 22 g, purified egg phospholipids 12 g, phosphate 15 mmol
Intralipid 30% (Fresenius Kabi) Net price 333 mL = £17.80	—	12600	—	—	—	—	—	soya oil 300 g, glycerol 16.7 g, purified egg phospholipids 12 g, phosphate 15 mmol
Lipofundin MCT/LCT 10% (B. Braun) Net price 100 mL = £7.70; 500 mL = £12.90	—	4430	—	—	—	—	—	soya oil 50 g, medium chain triglycerides 50 g
Lipofundin MCT/LCT 20% (B. Braun) Net price 100 mL = £12.51; 250 mL = £11.30; 500 mL = £19.18	—	8000	—	—	—	—	—	soya oil 100 g, medium chain triglycerides 100 g
³ Primene 10% (Baxter) Net price 100 mL = £5.78; 250 mL = £7.92	15	—	—	—	—	—	19	—
Synthamin 9 (Baxter) Net price 500 mL = £6.66; 1000 mL = £12.34	9.1	—	60	5	70	100	70	acid phosphate 30 mmol
Synthamin 9 EF (electrolyte-free) (Baxter) Net price 500 mL = £6.66; 1000 mL = £12.34	9.1	—	—	—	—	44	22	—
Vamin 9 Glucose (Fresenius Kabi) Net price 100 mL = £3.90; 500 mL = £7.95; 1000 mL = £13.80	9.4	1700	20	1.5	50	—	50	Ca ²⁺ 2.5 mmol, anhydrous glucose 100 g
³ Vaminolact (Fresenius Kabi) Net price 100 mL = £4.35; 500 mL = £10.00	9.3	—	—	—	—	—	—	—

1. Note. 1000 kcal = 4200 kJ; 1000 kJ = 238.8 kcal. All entries are (PoM)

2. Excludes protein- or amino acid-derived energy

3. For use in neonates and children only

Protein (nitrogen) is given as mixtures of essential and non-essential synthetic L-amino acids. Ideally, all essential amino acids should be included with a wide variety of non-essential ones to provide sufficient nitrogen together with electrolytes (see also section 9.2.2). Solutions vary in their composition of amino acids; they often contain an energy source (usually glucose) and electrolytes. Solutions for use in neonates and children under 1 year of age are based on the amino acid profile of umbilical cord blood (*Primene*®) or breast milk (*Vaminolact*®) and contain amino acids that are essential in this age group; these amino acids may not be present in sufficient quantities in preparations designed for older children and adults.

Energy requirements must be met if amino acids are to be utilised for tissue maintenance. An appropriate energy to protein ratio is essential and requirements will vary depending on the child's age and condition. A

mixture of carbohydrate and fat energy sources (usually 30–50% as fat) gives better utilisation of amino acids than glucose alone.

Glucose is the preferred source of carbohydrate, but frequent monitoring of blood glucose is required particularly during initiation and build-up of the regimen; insulin may be necessary. Glucose above a concentration of 12.5% must be infused through a central venous catheter to avoid thrombosis; the maximum concentration of glucose that should normally be infused in fluid restricted children is 20–25%.

In parenteral nutrition regimens, it is necessary to provide adequate **phosphate** in order to allow phosphorylation of glucose and to prevent hypophosphataemia. Neonates, particularly preterm neonates, and young children also require phosphorus and calcium to ensure adequate bone mineralisation. The compatibility and solubility of calcium and phosphorus salts is

complex and unpredictable; precipitation is a risk and specialist pharmacy advice should be sought.

Fat (lipid) emulsions have the advantages of a high energy to fluid volume ratio, neutral pH, and iso-osmolality with plasma, and provide essential fatty acids. Several days of adaptation may be required to attain maximal utilisation. Reactions include occasional febrile episodes (usually only with 20% emulsions) and rare anaphylactic responses. Interference with biochemical measurements such as those for blood gases and calcium may occur if samples are taken before fat has been cleared. Regular monitoring of plasma cholesterol and triglyceride is necessary to ensure clearance from the plasma, particularly in conditions where fat metabolism may be disturbed e.g. infection. Emulsions containing 20% or 30% fat should be used in neonates as they are cleared more efficiently. **Additives should not be mixed with fat emulsions unless compatibility is known.**

Electrolytes are usually provided as the chloride salts of potassium and sodium. Acetate salts can be used to reduce the amount of chloride infused; hyperchloraemic acidosis or hypochloraemic alkalosis can occur in pre-term neonates or children with renal impairment.

Administration. Because of the complex requirements relating to parenteral nutrition full details relating to administration have been omitted. In all cases *specialist pharmacy advice, product literature and other specialist literature should be consulted.*

Supplementary preparations

Compatibility with the infusion solution must be ascertained before adding supplementary preparations.

Addiphos® (Fresenius Kabi) (PoM)

Solution, sterile, phosphate 40 mmol, K^+ 30 mmol, Na^+ 30 mmol/20 mL. For addition to *Vamin*® solutions and glucose intravenous infusions. Net price 20-mL vial = £1.30

Additrace® (Fresenius Kabi) (PoM)

Solution, trace elements for addition to *Vamin*® solutions and glucose intravenous infusions, traces of Fe^{3+} , Zn^{2+} , Mn^{2+} , Cu^{2+} , Cr^{3+} , Se^{4+} , Mo^{6+} , F^- , I^- . For children over 40 kg. Net price 10-mL amp = £1.96

Cernevit® (Baxter) (PoM)

Solution, *dl*-alpha tocopherol 11.2 units, ascorbic acid 125 mg, biotin 69 micrograms, colexcalciferol 220 units, cyanocobalamin 6 micrograms, folic acid 414 micrograms, glycine 250 mg, nicotinamide 46 mg, pantothenic acid (as dexpantenol) 17.25 mg, pyridoxine hydrochloride 5.5 mg, retinol (as palmitate) 3500 units, riboflavin (as dihydrated sodium phosphate) 4.14 mg, thiamine (as cocarboxylase tetrahydrate) 3.51 mg. Dissolve in 5 mL water for injections. Net price per vial = £4.64

Decan® (Baxter) (PoM)

Solution, trace elements for addition to infusion solutions, Fe^{2+} , Zn^{2+} , Cu^{2+} , Mn^{2+} , F^- , Co^{2+} , I^- , Se^{4+} , Mo^{6+} , Cr^{3+} . For children over 40 kg. Net price 40-mL vial = £2.00

Dipeptiven® (Fresenius Kabi) (PoM)

Solution, *N*(2)-L-alanyl-L-glutamine 200 mg/mL (providing L-alanine 82 mg, L-glutamine 134.6 mg). For addition to infusion solutions containing amino acids. Net price 50 mL = £13.94, 100 mL = £25.93

Dose

Amino acid supplement for hypercatabolic or hyper-metabolic states

300–400 mg/kg daily; max. 400 mg/kg daily, dose not to exceed 20% of total amino acid intake

Glycophos® Sterile Concentrate (Fresenius Kabi) (PoM)

Solution, sterile, phosphate 20 mmol, Na^+ 40 mmol/20 mL. For addition to *Vamin*® and *Vaminolact*® solutions, and glucose intravenous infusions. Net price 20-mL vial = £3.91

Peditrace® (Fresenius Kabi) (PoM)

Solution, trace elements for addition to *Vaminolact*®, *Vamin*® 14 *Electrolyte-Free* solutions and glucose intravenous infusions, traces of Zn^{2+} , Cu^{2+} , Mn^{2+} , Se^{4+} , F^- , I^- . For use in neonates (when kidney function established, usually second day of life), infants, and children. Net price 10-mL vial = £3.55

Cautions reduced biliary excretion especially in cholestatic liver disease or in markedly reduced urinary excretion (careful biochemical monitoring required); total parenteral nutrition exceeding 1 month (measure serum manganese concentration and check liver function before commencing treatment and regularly during treatment)—discontinue if manganese concentration raised or if cholestasis develops

Solivito N® (Fresenius Kabi) (PoM)

Solution, powder for reconstitution, biotin 60 micrograms, cyanocobalamin 5 micrograms, folic acid 400 micrograms, glycine 300 mg, nicotinamide 40 mg, pyridoxine hydrochloride 4.9 mg, riboflavin sodium phosphate 4.9 mg, sodium ascorbate 113 mg, sodium pantothenate 16.5 mg, thiamine mononitrate 3.1 mg. Dissolve in water for injections or glucose intravenous infusion for adding to glucose intravenous infusion or *Intralipid*®; dissolve in *Vitlipid N*® or *Intralipid*® for adding to *Intralipid*® only. Net price per vial = £1.97

Vitlipid N® (Fresenius Kabi) (PoM)

Emulsion, adult, vitamin A 330 units, ergocalciferol 20 units, *dl*-alpha tocopherol 1 unit, phytomenadione 15 micrograms/mL. For addition to *Intralipid*®. For adults and children over 11 years. Net price 10-mL amp = £1.97

Emulsion, infant, vitamin A 230 units, ergocalciferol 40 units, *dl*-alpha tocopherol 0.7 unit, phytomenadione 20 micrograms/mL. For addition to *Intralipid*®. Net price 10-mL amp = £1.97

9.4 Oral nutrition

9.4.1 Foods for special diets

9.4.2 Enteral nutrition

9.4.1 Foods for special diets

These are preparations that have been modified to eliminate a particular constituent from a food or that are nutrient mixtures formulated as food substitutes for children who either cannot tolerate or cannot metabolise certain common constituents of food.

Coeliac disease Intolerance to gluten in coeliac disease is managed by completely eliminating gluten from the diet. A range of gluten-free products is available for prescription—see Appendix 2 (p. 808).

Phenylketonuria Phenylketonuria (hyperphenylalaninaemia, PKU), which results from the inability to metabolise phenylalanine, is managed by restricting dietary intake of phenylalanine to a small amount sufficient for tissue building and repair.

Aspartame (used as a sweetener in some foods and medicines) contributes to the phenylalanine intake and may affect control of phenylketonuria. If alternatives are unavailable, children with phenylketonuria should not be denied access to appropriate medication; the amount of aspartame consumed can be taken in to account in the management of the condition. Where the presence of aspartame in a preparation is specified in the product literature, aspartame is listed as an excipient in the relevant product entry in *BNF for Children*; the child or carer should be informed of this.

For further information on special dietary products used in the management of metabolic diseases, see Appendix 2.

Some rare forms of phenylketonuria are caused by a deficiency of tetrahydrobiopterin. Treatment involves oral supplementation of **tetrahydrobiopterin**; in some severe cases, the addition of the neurotransmitter precursors, levodopa (section 4.9.1) and 5-hydroxytryptophan, is also necessary.

Sapropterin, a synthetic form of tetrahydrobiopterin, is licensed as an adjunct to dietary restriction of phenylalanine in the management of patients with phenylketonuria and tetrahydrobiopterin deficiency.

TETRAHYDROBIOPTERIN

Renal impairment use with caution—accumulation of metabolites

Pregnancy crosses the placenta; use only if benefit outweighs risk

Breast-feeding present in milk, effects unknown

Side-effects diarrhoea, urinary frequency, disturbed sleep

Licensed use not licensed

Indications and dose

Monotherapy in tetrahydrobiopterin-sensitive phenylketonuria (specialist use only)

• By mouth

Child 1 month–18 years 10 mg/kg twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to response

In combination with neurotransmitter precursors for tetrahydrobiopterin-sensitive phenylketonuria (specialist use only)

• By mouth

Child 1 month–2 years initially 250–750 micrograms/kg 4 times daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to response; max. 7 mg/kg daily

Child 2–18 years initially 250–750 micrograms/kg 4 times daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to response; usual max. 10 mg/kg daily

Tetrahydrobiopterin (Non-proprietary)

Tablets, tetrahydrobiopterin 10 mg and 50 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

SAPROPTERIN DIHYDROCHLORIDE

Note Sapropterin is a synthetic form of tetrahydrobiopterin

Cautions monitor blood-phenylalanine concentration before and after first week of treatment—if unsatisfactory response increase dose at weekly intervals to max. dose and monitor blood-phenylalanine concentration weekly; discontinue treatment if unsatisfactory response after 1 month; monitor blood-phenylalanine and tyrosine concentrations 1–2 weeks after dose adjustment and during treatment; history of convulsions

Hepatic impairment manufacturer advises caution—no information available

Renal impairment manufacturer advises caution—no information available

Pregnancy manufacturer advises caution—consider only if strict dietary management inadequate

Breast-feeding manufacturer advises avoid—no information available

Side-effects diarrhoea, vomiting, abdominal pain, nasal congestion, cough, pharyngolaryngeal pain, headache; also reported hypersensitivity reactions

Indications and dose

Phenylketonuria (specialist use only)

• By mouth

Child 4–18 years initially 10 mg/kg once daily, preferably in the morning, adjusted according to response; usual dose 5–20 mg/kg daily

Tetrahydrobiopterin deficiency (specialist use only)

• By mouth

Neonate initially 2–5 mg/kg once daily, preferably in the morning, adjusted according to response; max. 20 mg/kg daily; total daily dose may alternatively be given in 2–3 divided doses

Child 1 month–18 years initially 2–5 mg/kg once daily, preferably in the morning, adjusted according to response; max. 20 mg/kg daily; total daily dose may alternatively be given in 2–3 divided doses

Kuvan® (Merck Serono) (POM)

Dispersible tablets, sapropterin dihydrochloride 100 mg, net price 30-tab pack = £597.22, 120-tab pack = £2388.88. Label: 13, 21, counselling, tablets should be dissolved in water and taken within 20 minutes

9.4.2 Enteral nutrition

Children have higher nutrient requirements per kg body-weight, different metabolic rates, and physiological responses compared to adults. They have low nutritional stores and are particularly vulnerable to growth and nutritional problems during critical periods of development. Major illness, operations, or trauma impose increased metabolic demands and can rapidly exhaust nutritional reserves.

Every effort should be made to optimise oral food intake before beginning enteral tube feeding; this may include change of posture, special seating, feeding equipment,

oral desensitisation, food texture changes, thickening of liquids, increasing energy density of food, treatment of reflux or oesophagitis, as well as using age-specific nutritional supplements.

Enteral tube feeding has a role in both short-term rehabilitation and long-term nutritional management in paediatrics. It can be used as supportive therapy, in which the enteral feed supplies a proportion of the required nutrients, or as primary therapy, in which the enteral feed delivers all the necessary nutrients. Most children receiving tube feeds should also be encouraged to take oral food and drink. Tube feeding should be considered in the following situations:

- unsafe swallowing and risk of aspiration;
- inability to consume at least 60% of energy needs by mouth;
- total feeding time of more than 4 hours per day;
- weight loss or no weight gain for a period of 3 months (less for younger children and infants);
- weight for height (or length) less than 2nd percentile for age and sex.

Most feeds for enteral use (Appendix 2) contain protein derived from cows' milk or soya. Elemental feeds containing protein hydrolysates or free amino acids can be used for children who have diminished ability to break down protein, for example in inflammatory bowel disease or pancreatic insufficiency.

Even when nutritionally complete feeds are given, water and electrolyte balance should be monitored. Haematological and biochemical parameters should also be monitored, particularly in the clinically unstable child. Extra minerals (e.g. magnesium and zinc) may be needed in patients where gastro-intestinal secretions are being lost. Additional vitamins may also be needed. Feeds containing vitamin K may affect the INR in children receiving warfarin—see **interactions**: Appendix 1 (vitamins).

Choosing the best formula for children depends on several factors including: nutritional requirements, gastro-intestinal function, underlying disease, nutrient restrictions, age, and feed characteristics (nutritional composition, viscosity, osmolality, availability and cost). Children have specific dietary requirements and in many situations liquid feeds prepared for adults are totally unsuitable and should not be given. Expert advice from a dietician should be sought before prescribing enteral feeds for a child.

Infant formula feeds Child 0–12 months. Term infants with normal gastro-intestinal function are given either breast milk or normal infant formula during the first year of life. The average intake is between 150 mL and 200 mL/kg/day. Infant milk formulas are based on whey- or casein-dominant protein, lactose with or without maltodextrin, amylose, vegetable oil and milk fat. The composition of all normal and soya infant formulas have to meet The Infant Formula and Follow-on Formula Regulations (England and Wales) 2007, which enact the European Community Regulations 2006/141/EC; the composition of other enteral and specialist feeds has to meet the Commission Directive (1999/21/EC) on Dietary Foods for Special Medical Purposes.

A high-energy feed (Appendix 2, p. 778), which contains 9–11% of energy derived from protein can be used for infants who fail to grow adequately. Alternatively,

energy supplements (Appendix 2, p. 801) may be added to normal infant formula to achieve a higher energy content (but this will reduce the protein to energy ratio) or the normal infant formula concentration may be increased slightly. Care should be taken not to present an osmotic load of more than 500 milliosmoles/kg water to the normal functioning gut, otherwise osmotic diarrhoea will result. Concentrating or supplementing feeds should not be attempted without the advice of a paediatric dietician.

Enteral feeds Child 1–6 years (body-weight 8–20 kg). Ready-to-use feeds (Appendix 2, p. 778) based on caseinates, maltodextrin and vegetable oils (with or without added medium chain triglyceride (MCT) oil or fibre) are well tolerated and effective in improving nutritional status in this age group. Although originally designed for children 1–6 years (body-weight 8–20 kg), some products have ACBS approval for use in children weighing up to 30 kg (approx. 10 years of age). Enteral feeds formulated for children 1–6 years are low in sodium and potassium; electrolyte intake and biochemical status should be monitored. Older children in this age range taking small feed volumes may need to be given additional micronutrients. Fibre-enriched feeds may be helpful for children with chronic constipation or diarrhoea.

Child 7–12 years (body-weight 21–45 kg). Depending on age, weight, clinical condition and nutritional requirements, ready-to-use feeds (Appendix 2, p. 778) formulated for 7–12 year olds may be given at appropriate rates.

Child over 12 years (body-weight over 45 kg). As there are no standard enteral feeds formulated for this age group, adult formulations are used. The intake of protein, electrolytes, vitamins, and trace minerals should be carefully assessed and monitored.

Note Adult feeds containing more than 6 g/100 mL protein or 2 g/100 mL fibre should be used with caution and expert advice.

Specialised formula It is essential that any infant who is intolerant of breast milk or normal infant formula, or whose condition requires nutrient-specific adaptation, is prescribed an adequate volume of a nutritionally complete replacement formula (see Appendix 2, p. 790). In the first 4 months of life, a volume of 150–200 mL/kg/day is recommended. After 6 months, should the formula still be required, a volume of 600 mL/day should be maintained, in addition to solid food.

Products for cow's milk protein intolerance or lactose intolerance. There are a number of infant formulas formulated for cow's milk protein intolerance or lactose intolerance; these feeds may contain a residual amount of lactose (less than 1 g/100 mL formula)—sometimes described as clinically lactose-free or 'lactose-free' by manufacturers. If the total daily intake of these formulas is low, it may be necessary to supplement with calcium, and a vitamin and mineral supplement.

Soya-based infant formulas have a high phytoestrogen content and this may be a long-term reproductive health risk. The Chief Medical Officer has advised that soya-based infant formulas should not be used as the first choice for the management of infants with proven cow's milk sensitivity, lactose intolerance, galactokinase deficiency and galactosaemia. Most UK paediatricians with expertise in inherited metabolic disease still advocate soya-based formulations for infants with galactosaemia as there are concerns about the residual lactose content

of low lactose formulas and protein hydrolysates based on cow's milk protein.

Low lactose infant formulations, based on whole cow's milk protein, are unsuitable for children with cow's milk protein intolerance. Liquid soya milks purchased from supermarkets and health food stores are not nutritionally complete and should never be used for infants under 1 year of age.

Protein hydrolysate formulas. Non-milk, peptide-based feeds containing hydrolysates of casein, whey, meat and soya protein, are suitable for infants with disaccharide or whole protein intolerance. The total daily intake of electrolytes, vitamins and minerals should be carefully assessed and modified to meet the child's nutritional requirements; these feeds have a high osmolality when given at recommended dilution and need gradual and careful introduction.

Elemental (amino acid based formula). Specially formulated elemental feeds containing essential and non-essential amino acids are available for use in infants and children under 6 years with proven whole protein intolerance. Adult elemental formula may be used for children over 6 years; the intake of electrolytes, vitamins and minerals should be carefully assessed and modified to meet nutritional requirements. These feeds have a high osmolality when given at the recommended concentration and therefore need gradual and careful introduction.

Modular feeds. Modular feeds (see Specialised Formulas for Specific Clinical Conditions, p. 800) are based on individual protein, fat, carbohydrate, vitamin and mineral components or modules which can be combined to meet the specific needs of a child. Modular feeds are used when nutritionally complete specialised formula are not tolerated, or if the fluid and nutrient requirements change e.g. in gastro-intestinal, renal or liver disease. The main advantage of modular feeds is their flexibility; disadvantages include their complexity and preparation difficulties. Modular feeds should not be used without the supervision of a paediatric dietician.

Specialised formula. Highly specialised formulas are designed to meet the specific requirements in various clinical conditions such as renal and liver diseases. When using these formulas, both the biochemical status of the child and their growth parameters need to be monitored.

Feed thickeners Carob based thickeners (Appendix 2, p. 807) may be used to thicken feeds for infants under 1 year with significant gastro-oesophageal reflux. Breast-fed infants can be given the thickener mixed to a paste with water or breast-milk prior to feeds.

Pre-thickened formula Milk-protein- or casein-dominant infant formula, which contains small quantities of pre-gelatinized starch, is recommended primarily for infants with mild gastro-oesophageal reflux. Pre-thickened formula is prepared in the same way as normal infant formula and flows through a standard teat. The feeds do not thicken on standing but thicken in the stomach when exposed to acid pH.

Starched based thickeners can be used to thicken liquids and feeds for children over 1 year of age with dysphagia.

Dietary supplements for oral use (Appendix 2, p. 783) Three types of prescribable fortified dietary supplements are available: fortified milk and non-milk

tasting (juice-style) drinks, and fortified milk-based semi-solid preparations. The recommended daily quantity is age-dependent. The following is a useful guide: 1–2 years, 200 kcal (840 kJ); 3–5 years, 400 kcal (1680 kJ); 6–11 years, 600 kcal (2520 kJ); and over 12 years, 800 kcal (3360 kJ). Supplements containing 1.5 kcal/mL are high in protein and should not be used for children under 3 years of age. Many supplements are high in sugar or maltodextrin; care should be taken to prevent prolonged contact with teeth. Ideally supplements should be administered after meals or at bedtime so as not to affect appetite.

Products for metabolic diseases There is a large range of disease-specific infant formulas and amino acid-based supplements available for use in children with metabolic diseases (see under specific metabolic diseases, Appendix 2, p. 811). Some of these formulas are nutritionally incomplete and supplementation with vitamins and other nutrients may be necessary. Many of the product names are similar; to prevent metabolic complications in children who cannot tolerate specific amino acids it is important to ensure the correct supplement is supplied.

Preparations (Borderline substances) See Appendix 2.

9.5 Minerals

9.5.1 Calcium and magnesium

9.5.2 Phosphorus

9.5.3 Fluoride

9.5.4 Zinc

See section 9.1.1 for iron salts.

9.5.1 Calcium and magnesium

9.5.1.1 Calcium supplements

9.5.1.2 Hypercalcaemia and hypercalciuria

9.5.1.3 Magnesium

9.5.1.1 Calcium supplements

Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary requirement varies with age and is relatively greater in childhood, pregnancy, and lactation, due to an increased demand. Hypocalcaemia may be caused by vitamin D deficiency (section 9.6.4), impaired metabolism, a failure of secretion (hypoparathyroidism), or resistance to parathyroid hormone (pseudohypoparathyroidism).

Mild asymptomatic hypocalcaemia may be managed with oral calcium supplements. *Severe symptomatic hypocalcaemia* requires an intravenous infusion of calcium gluconate 10% over 5 to 10 minutes, repeating the dose if symptoms persist; in exceptional cases it may be necessary to maintain a continuous calcium infusion over a day or more. Calcium chloride injection is also available, but is more irritant; care should be taken to prevent extravasation.

For the role of calcium gluconate in temporarily reducing the toxic effects of *hypercalcaemia*, see p. 464.

Persistent hypocalcaemia requires oral calcium supplements and either a vitamin D analogue (alfacalcidol or

calcitriol) for hypoparathyroidism and pseudohypoparathyroidism or natural vitamin D (calciferol) if due to vitamin D deficiency (section 9.6.4). It is important to monitor plasma and urinary calcium during long-term maintenance therapy.

Neonates Hypocalcaemia is common in the first few days of life, particularly following birth asphyxia or respiratory distress. Late onset at 4–10 days after birth may be secondary to vitamin D deficiency, hypoparathyroidism or hypomagnesaemia and may be associated with seizures.

CALCIUM SALTS

Cautions see notes above; sarcoidosis; history of nephrolithiasis; avoid calcium chloride in respiratory acidosis or respiratory failure; **interactions:** Appendix 1 (antacids, calcium salts)

Contra-indications conditions associated with hypercalcaemia and hypercalciuria (e.g. some forms of malignant disease); see also Calcium Gluconate injection, p. 478

Renal impairment use with caution; risk of hypercalcaemia and renal calculi

Side-effects rarely gastro-intestinal disturbances; with injection, bradycardia, arrhythmias, peripheral vasodilatation, fall in blood pressure, sweating, injection-site reactions, severe tissue damage with extravasation

Indications and dose

See notes above; calcium deficiency

• By mouth

Neonate 0.25 mmol/kg 4 times a day, adjusted to response

Child 1 month–4 years 0.25 mmol/kg 4 times a day, adjusted to response

Child 5–12 years 0.2 mmol/kg 4 times a day, adjusted to response

Child 12–18 years 10 mmol 4 times a day, adjusted to response

Acute hypocalcaemia, urgent correction; hyperkalaemia (prevention of arrhythmias)

• By slow intravenous injection over 5–10 minutes

Neonate 0.11 mmol/kg (0.5 mL/kg of calcium gluconate 10%) as a single dose. [Some units use a dose of 0.46 mmol/kg (2 mL/kg calcium gluconate 10%) for hypocalcaemia in line with US practice]

Child 1 month–18 years 0.11 mmol/kg (0.5 mL/kg calcium gluconate 10%), max 4.5 mmol (20 mL calcium gluconate 10%)

Acute hypocalcaemia, maintenance

• By continuous intravenous infusion

Neonate 0.5 mmol/kg daily over 24 hours, adjusted to response, use oral route as soon as possible due to risk of extravasation

Child 1 month–2 years 1 mmol/kg daily (usual max 8.8 mmol) over 24 hours, use oral route as soon as possible due to risk of extravasation

Child 2–18 years 8.8 mmol over 24 hours, use oral route as soon as possible due to risk of extravasation

Oral preparations

Calcium Gluconate (Non-proprietary)

Effervescent tablets, calcium gluconate 1 g (calcium 89 mg or Ca^{2+} 2.23 mmol), net price 28-tab pack = £14.82. Label: 13

Note Each tablet usually contains 4.46 mmol Na^{+}

Calcium Lactate (Non-proprietary)

Tablets, calcium lactate 300 mg (calcium 39 mg or Ca^{2+} 1 mmol), net price 84 = £4.57

Adcal[®] (ProStrakan)

Chewable tablets, fruit flavour, calcium carbonate 1.5 g (calcium 600 mg or Ca^{2+} 15 mmol), net price 100-tab pack = £8.70. Label: 24

Cacit[®] (Warner Chilcott)

Tablets, effervescent, pink, calcium carbonate 1.25 g, providing calcium citrate when dispersed in water (calcium 500 mg or Ca^{2+} 12.5 mmol), net price 76-tab pack = £11.81. Label: 13

Calcichew[®] (Takeda)

Tablets (chewable), orange flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca^{2+} 12.5 mmol), net price 100-tab pack = £9.33. Label: 24

Forté tablets (chewable), orange flavour, scored, calcium carbonate 2.5 g (calcium 1 g or Ca^{2+} 25 mmol), net price 60-tab pack = £13.16. Label: 24

Excipients include aspartame (section 9.4.1)

Calcium-500 (Martindale)

Tablets, pink, f/c, calcium carbonate 1.25 g (calcium 500 mg or Ca^{2+} 12.5 mmol), net price 100-tab pack = £9.46. Label: 25

Calcium-Sandoz[®] (Alliance)

Syrup, orange flavour, calcium gluconate 1.09 g, calcium lactobionate 727 mg (calcium 108.3 mg or Ca^{2+} 2.7 mmol)/5 mL, net price 300 mL = £4.07

Sandocal[®] (Novartis Consumer Health)

Sandocal 1000 tablets, effervescent, orange flavour, calcium lactate gluconate 2.263 g, calcium carbonate 1.75 g, providing 1 g calcium (Ca^{2+} 25 mmol), net price 3 × 10-tab pack = £6.91. Label: 13

Excipients include aspartame (section 9.4.1)

Parenteral preparations

Calcium Gluconate (Non-proprietary) ^(PoM)

Injection, calcium gluconate 10% (Ca^{2+} approx. 225 micromol/mL). Net price 10-mL amp = 65p

Administration For intravenous infusion dilute to at least 45 micromol/mL with Glucose 5% or Sodium Chloride 0.9%. Maximum administration rate 45 micromol/kg/hour (or in neonates max. 22 micromol/kg/hour). May be given more concentrated via a central venous catheter. May be used undiluted (10% calcium gluconate) in emergencies. Avoid extravasation; should not be given by intramuscular injection. Incompatible with sodium bicarbonate and phosphate solutions.

Note The MHRA has advised that repeated or prolonged administration of calcium gluconate injection packaged in 10 mL glass containers is contra-indicated in children under 18 years and in patients with renal impairment owing to the risk of aluminium accumulation; in these patients the use of calcium gluconate injection packaged in plastic containers is recommended

Calcium Chloride (Non-proprietary) (PoM)

Injection, calcium chloride dihydrate 10% (calcium 27.3 mg or Ca^{2+} 680 micromol/mL), net price 10-mL disposable syringe = £6.94

Brands include Minijet® Calcium Chloride 10%

Injection, calcium chloride dihydrate 13.4% (calcium 36 mg or Ca^{2+} 910 micromol/mL), net price 10-mL amp = £14.94

■ **With vitamin D**

Section 9.6.4

9.5.1.2 Hypercalcaemia and hypercalciuria

Severe hypercalcaemia Severe hypercalcaemia calls for urgent treatment before detailed investigation of the cause. Dehydration should be corrected first with intravenous infusion of **sodium chloride 0.9%**. Drugs (such as thiazides and vitamin D compounds) which promote hypercalcaemia, should be discontinued and dietary calcium should be restricted.

If severe hypercalcaemia persists drugs which inhibit mobilisation of calcium from the skeleton may be required. The **bisphosphonates** are useful and pamidronate disodium (section 6.6.2) is probably the most effective.

Corticosteroids (section 6.3) are widely given, but may only be useful where hypercalcaemia is due to sarcoidosis or vitamin D intoxication; they often take several days to achieve the desired effect.

Calcitonin (section 6.6.1) can be used by specialists for the treatment of hypercalcaemia associated with malignancy; it is rarely effective where bisphosphonates have failed to reduce serum calcium adequately.

After treatment of severe hypercalcaemia the underlying cause must be established. Further treatment is governed by the same principles as for initial therapy. Salt and water depletion and drugs promoting hypercalcaemia should be avoided; oral administration of a bisphosphonate may be useful. Parathyroidectomy may be indicated for hyperparathyroidism.

Hypercalciuria Hypercalciuria should be investigated for an underlying cause, which should be treated. Reducing dietary calcium intake may be beneficial but severe restriction of calcium intake has not proved beneficial and may even be harmful.

9.5.1.3 Magnesium

Magnesium is an essential constituent of many enzyme systems, particularly those involved in energy generation; the largest stores are in the skeleton.

Magnesium salts are not well absorbed from the gastrointestinal tract, which explains the use of magnesium sulfate (section 1.6.4) as an osmotic laxative.

Magnesium is excreted mainly by the kidneys and is therefore retained in renal failure, but significant *hypomagnesaemia* (causing muscle weakness and arrhythmias) is rare.

Hypomagnesaemia Since magnesium is secreted in large amounts in the gastro-intestinal fluid, excessive losses in diarrhoea, stoma or fistula are the most common causes of *hypomagnesaemia*; deficiency may also occur as a result of treatment with certain drugs. Hypo-

magnesaemia often causes secondary hypocalcaemia (with which it may be confused), particularly in neonates, and also hypokalaemia and hyponatraemia.

Symptomatic *hypomagnesaemia* is associated with a deficit of 0.5–1 mmol/kg. Magnesium is given initially by intravenous infusion or by intramuscular injection of **magnesium sulfate**; the intramuscular injection is painful. Plasma magnesium concentration should be measured to determine the rate and duration of infusion and the dose should be reduced in renal impairment. To prevent recurrence of the deficit, magnesium may be given by mouth in divided doses, but there is limited evidence of benefit. For maintenance (e.g. in intravenous nutrition), parenteral doses of magnesium are of the order of 0.2–0.4 mmol/kg (usual max. 20 mmol) Mg^{2+} daily.

Arrhythmias Magnesium sulfate injection has also been recommended for the emergency treatment of serious arrhythmias, especially in the presence of hypokalaemia (when hypomagnesaemia may also be present) and when salvos of rapid ventricular tachycardia show the characteristic twisting wave front known as *torsade de pointes* (see also section 2.3.1).

MAGNESIUM SULFATE

Note Magnesium Sulfate Injection BP is a sterile solution of Magnesium Sulfate Heptahydrate

Cautions see notes above; in severe hypomagnesaemia administer initially via controlled infusion device (preferably syringe pump); monitor blood pressure, respiratory rate, urinary output and for signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, drowsiness, double vision, and slurred speech); **interactions:** Appendix 1 (magnesium, parenteral)

Hepatic impairment avoid in hepatic coma if risk of renal failure

Renal impairment avoid or reduce dose; increased risk of toxicity

Pregnancy sufficient may cross the placenta in mothers treated with high doses e.g. in pre-eclampsia, causing hypotonia and respiratory depression in newborns

Side-effects generally associated with hypermagnesaemia, nausea, vomiting, thirst, flushing of skin, hypotension, arrhythmias, coma, respiratory depression, drowsiness, confusion, loss of tendon reflexes, muscle weakness

Indications and dose

Neonatal hypocalcaemia

- By deep intramuscular injection or intravenous infusion

Neonate 0.4 mmol/kg Mg^{2+} (100 mg/kg magnesium sulfate heptahydrate) 12 hourly for 2–3 doses

Hypomagnesaemia

- By intravenous injection over at least 10 minutes

Neonate 0.4 mmol/kg Mg^{2+} (100 mg/kg magnesium sulfate heptahydrate) 6–12 hourly as necessary

Child 1 month–12 years 0.2 mmol/kg Mg^{2+} (50 mg/kg magnesium sulfate heptahydrate) 12 hourly as necessary

Child 12–18 years 4 mmol Mg^{2+} (1 g magnesium sulfate heptahydrate) 12 hourly as necessary

Torsade de pointes (consult local guidelines)

- By intravenous injection over 10–15 minutes

Child 1 month–18 years 0.1–0.2 mmol/kg (25–50 mg/kg magnesium sulfate heptahydrate); max. 8 mmol (2 g magnesium sulfate heptahydrate); dose repeated once if necessary

Persistent pulmonary hypertension section 2.5.1

Severe acute asthma section 3.1

Administration Dilute to 10% (100 mg magnesium sulfate heptahydrate (0.4 mmol Mg^{2+}) in 1 mL) with Glucose 5 or 10%, Sodium Chloride 0.45 or 0.9% or Glucose and Sodium Chloride combinations. Up to 20% solution may be given in fluid restriction. Rate of administration should not exceed 10 mg/kg/minute (0.04 mmol/kg/minute Mg^{2+}) of magnesium sulfate heptahydrate

Note Magnesium sulfate heptahydrate 1 g equivalent to Mg^{2+} approx. 4 mmol

Magnesium Sulfate Injection, BP (Non-proprietary) (PoM)

Injection, magnesium sulfate heptahydrate 20% (Mg^{2+} approx. 0.8 mmol/mL), net price 20-mL (4-g) amp = £16.98; 50% (Mg^{2+} approx. 2 mmol/mL), 2-mL (1-g) amp = £1.09, 4-mL (2-g) prefilled syringe = £10.23; 5-mL (2.5-g) amp = £5.56, 10-mL (5-g) amp = £1.46; 10-mL (5-g) prefilled syringe = £4.95
Brands include Minijet® Magnesium Sulfate Injection BP 50%

Note The BP directs that the label states the strength as the % w/v of magnesium sulfate heptahydrate and as the approximate concentration of magnesium ions (Mg^{2+}) in mmol/mL

MAGNESIUM-L-ASPARTATE

Cautions see under Magnesium Sulfate

Renal impairment avoid or reduce dose; increased risk of toxicity

Side-effects see under Magnesium Sulfate; also diarrhoea

Licensed use classified as a Food for Special Medical Purposes for use in children over 2 years

Indications and dose

Hypomagnesaemia (but see notes above)

- By mouth

Child 1 month–2 years initially 0.2 mmol/kg of Mg^{2+} 3 times daily dissolved in water, dose adjusted as required

Child 2–10 years half a sachet (5 mmol Mg^{2+}) daily dissolved in 100 mL of water, dose adjusted as required

Child 10–18 years one sachet (10 mmol Mg^{2+}) daily dissolved in 200 mL of water, dose adjusted as required

Magnaspartate® (KoRa)

Oral powder, magnesium-L-aspartate 6.5 g (10 mmol Mg^{2+})/sachet, net price 10-sachet pack = £7.95

Excipients include sucrose

MAGNESIUM GLYCEROPHOSPHATE

Cautions see under Magnesium Sulfate

Renal impairment avoid or reduce dose; increased risk of toxicity

Side-effects see under Magnesium Sulfate; also diarrhoea

Licensed use not licensed

Indications and dose

Hypomagnesaemia (but see notes above)

- By mouth

Child 1 month–12 years initially 0.2 mmol/kg Mg^{2+} 3 times daily, dose adjusted as required

Child 12–18 years initially 4–8 mmol Mg^{2+} 3 times daily, dose adjusted as required

Administration tablets may be dispersed in water

Magnesium Glycerophosphate (Non-proprietary)

Tablets, magnesium glycerophosphate 1 g (approximately magnesium 97 mg or Mg^{2+} 4 mmol)

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Liquid, magnesium glycerophosphate 250 mg/mL (approximately magnesium 24.25 mg or Mg^{2+} 1 mmol/mL)

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

9.5.2 Phosphorus

9.5.2.1 Phosphate supplements

9.5.2.2 Phosphate-binding agents

9.5.2.1 Phosphate supplements

Oral phosphate supplements may be required in addition to vitamin D in children with hypophosphataemic vitamin D-resistant rickets (section 9.6.4). Diarrhoea is a common side-effect and should prompt a reduction in dosage.

Phosphate infusion is occasionally needed in phosphate deficiency arising from use of parenteral nutrition deficient in phosphate supplements; phosphate depletion also occurs in severe diabetic ketoacidosis. It is difficult to provide detailed guidelines for the treatment of *severe hypophosphatemia* because the extent of total body deficits and response to therapy are difficult to predict. High doses of phosphate may result in a transient serum elevation followed by redistribution into intracellular compartments or bone tissue; excessive doses may cause hypocalcaemia and metastatic calcification. It is essential to monitor plasma concentrations of calcium, phosphate, potassium and other electrolytes. It is recommended that severe hypophosphataemia be treated intravenously as large doses of oral phosphate may cause diarrhoea; intestinal absorption may be unreliable and dose adjustment may be necessary.

Phosphate is not the first choice for the treatment of hypercalcaemia because of the risk of precipitation of calcium phosphate in the kidney and other tissues. If used, the child should be well hydrated and electrolytes monitored.

Neonates Phosphate deficiency may occur in very low-birthweight infants and may compromise bone growth if not corrected. Parenterally fed infants may be at risk of phosphate deficiency due to the limited solubility of phosphate. Some units routinely supplement expressed breast milk with phosphate, although the effect on the osmolality of the milk should be considered.

PHOSPHATE

Cautions see notes above, also cardiac disease, diabetes mellitus, dehydration; avoid extravasation with parenteral forms, severe tissue necrosis; sodium and potassium concentrations of preparations

Renal impairment reduce dose; monitor closely

Side-effects nausea, diarrhoea; hypotension, oedema; hypocalcaemia; acute renal failure; phlebitis; tissue necrosis on extravasation

Indications and dose

Hypophosphataemia, including hypophosphataemic rickets and osteomalacia (see notes above)

• By mouth

Neonate 1 mmol/kg daily in 1–2 divided doses, or as a supplement in breast milk

Child 1 month–5 years 2–3 mmol/kg (max. 48 mmol) phosphate daily in 2–4 divided doses, adjusted as necessary

Child 5–18 years 2–3 mmol/kg (max. 97 mmol) phosphate daily in 2–4 divided doses, adjusted as necessary

Administration Caution, solubility in breast milk is limited to 1.2 mmol in 100 mL if calcium also added, contact pharmacy department for details

• By intravenous infusion (see notes above, administration below, and seek specialist advice)

Neonate 1 mmol/kg phosphate daily, adjusted as necessary

Child 1 month–2 years 0.7 mmol/kg phosphate daily, adjusted as necessary

Child 2–18 years 0.4 mmol/kg phosphate daily, adjusted as necessary

Administration (see also Important, below) Dilute injection with Sodium Chloride 0.9% or 0.45% or Glucose 5% or 10%. Administration rate of phosphate should not exceed 0.05 mmol/kg/hour. In emergencies in intensive care faster rates may be used—seek specialist advice

Important

Some phosphate injection preparations also contain potassium. For peripheral intravenous administration the concentration of potassium should not usually exceed 40 mmol/litre. The infusion solution should be **thoroughly mixed**. Local policies on avoiding inadvertent use of potassium concentrate should be followed. The potassium content of some phosphate preparations may also limit the rate at which they may be administered, see section 9.2.2.1.

Oral

Phosphate-Sandoz® (HK Pharma)

Tablets, effervescent, anhydrous sodium acid phosphate 1.936 g, sodium bicarbonate 350 mg, potassium bicarbonate 315 mg, equivalent to phosphorus 500 mg (phosphate 16.1 mmol), sodium 468.8 mg (Na^+ 20.4 mmol), potassium 123 mg (K^+ 3.1 mmol). Net price 20 = £3.29. Label: 13

Injection

Phosphates (Fresenius Kabl) (PoM)

Intravenous infusion, phosphates (providing phosphate 100 mmol/litre, potassium 19 mmol/litre, sodium 162 mmol/litre), net price 500 mL (*Polyfusor®*) = £53.40.

Potassium acid phosphate (Non-proprietary) (PoM)

Injection, 13.6% (1 mmol/mL phosphate, 1 mmol/mL potassium) 10 mL ampoule

Note See also Important, p. 481

Dipotassium hydrogen phosphate (Non-proprietary) (PoM)

Injection, 17.42% (1 mmol/mL phosphate and 2 mmol/mL potassium) 10 mL ampoule

Note See also Important, p. 481

Disodium hydrogen phosphate (Non-proprietary) (PoM)

Injection, 17.42% (0.6 mmol/mL phosphate and 1.2 mmol/mL sodium) 10 mL ampoule

9.5.2.2 Phosphate-binding agents

Calcium-containing preparations are used as phosphate-binding agents in the management of hyperphosphataemia complicating renal failure. Aluminium-containing preparations are rarely used as phosphate-binding agents and can cause aluminium accumulation.

Sevelamer hydrochloride is licensed for the treatment of hyperphosphataemia in adults on haemodialysis or peritoneal dialysis. Although experience is limited in children sevelamer may be useful when hypercalcaemia prevents the use of calcium carbonate.

ALUMINIUM HYDROXIDE

Cautions see notes above; **interactions:** Appendix 1 (antacids)

Side-effects constipation; hyperaluminemia

Alu-Cap® (Meda)

Capsules, green/red, dried aluminium hydroxide 475 mg (low Na^+), net price 120-cap pack = £13.71

Dose

Hyperphosphataemia

• By mouth

Child 5–12 years 1–2 capsules 3–4 times daily, adjusted as necessary

Child 12–18 years 1–5 capsules 3–4 times daily, adjusted as necessary

CALCIUM SALTS

Cautions **interactions:** Appendix 1 (antacids, calcium salts)

Contra-indications hypercalcaemia, hypercalciuria

Side-effects hypercalcaemia

Indications and dose

Phosphate binding in renal failure and hyperphosphataemia

• By mouth

Child 1 month–1 year 120 mg calcium carbonate 3–4 times daily with feeds, adjusted as necessary

Child 1–6 years 300 mg calcium carbonate 3–4 times daily prior to or with meals, adjusted as necessary

Child 6–12 years 600 mg calcium carbonate 3–4 times daily prior to or with meals, adjusted as necessary

Child 12–18 years 1.25 g calcium carbonate 3–4 times daily prior to or with meals, adjusted as necessary

Adcal®

Section 9.5.1.1

Calcichew®

Section 9.5.1.1

Calcium-500

Section 9.5.1.1

Phosex® (Pharmacosmos)

Tablets, yellow, scored, calcium acetate 1 g (calcium 250 mg or Ca^{2+} 6.2 mmol), net price 180-tab pack = £19.79. Counselling, tablets can be broken to aid swallowing but not chewed (bitter taste), take with meals

Dose

Phosphate-binding agent (with meals) in renal failure, according to the requirements of the patient

SEVELAMER HYDROCHLORIDE

Cautions gastro-intestinal disorders; **interactions:** Appendix 1 (sevelamer)

Contra-indications bowel obstruction

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises use only if potential benefit outweighs risk

Side-effects nausea, vomiting, abdominal pain, constipation, diarrhoea, dyspepsia, flatulence; *very rarely* intestinal obstruction; *also reported* intestinal perforation, ileus, diverticulitis, pruritus, and rash

Licensed use not licensed for use in children under 18 years

Indications and dose

Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis

- By mouth

Child 12–18 years initially 0.8–1.6 g 3 times daily with meals, then adjusted according to plasma-phosphate concentration

Renagel® (Sanofi-Aventis) (PoM)

Tablets, f/c, sevelamer hydrochloride 800 mg, net price 180-tab pack = £167.04. Label: 25, counselling, with meals

Excipients include propylene glycol (see Excipients, p. 2)

9.5.3 Fluoride

Availability of adequate fluoride confers significant resistance to dental caries. It is now considered that the topical action of fluoride on enamel and plaque is more important than the systemic effect.

When the fluoride content of drinking water is less than 700 micrograms per litre (0.7 parts per million), daily administration of fluoride tablets or drops provide suitable supplementation. Systemic fluoride supplements should not be prescribed without reference to the fluoride content of the local water supply. Infants need not receive fluoride supplements until the age of 6 months.

Dentifrices which incorporate sodium fluoride or monofluorophosphate are also a convenient source of fluoride.

Individuals who are either particularly caries prone or medically compromised may be given additional protection by use of fluoride rinses or by application of

fluoride gels. Rinses may be used daily or weekly; daily use of a less concentrated rinse is more effective than weekly use of a more concentrated one. High-strength gels must be applied regularly under professional supervision; extreme caution is necessary to prevent the child from swallowing any excess. Less concentrated gels are available for home use. Varnishes are also available and are particularly valuable for young or disabled children since they adhere to the teeth and set in the presence of moisture.

Fluoride mouthwash, oral drops, tablets, and toothpaste are prescribable on form FP10D (GP14 in Scotland, WP10D in Wales; for details see preparations below).

There are also arrangements for health authorities to supply fluoride tablets in the course of pre-school dental schemes, and they may also be supplied in school dental schemes.

Fluoride gels are not prescribable on form FP10D (GP14 in Scotland, WP10D in Wales).

FLUORIDES

Note Sodium fluoride 2.2 mg provides approx. 1 mg fluoride ion

Contra-indications not for areas where drinking water is fluoridated

Side-effects occasional white flecks on teeth with recommended doses; *rarely* yellowish-brown discoloration if recommended doses are exceeded

Indications and dose

Dose expressed as fluoride ion (F^-)

Prophylaxis of dental caries—see notes above

Water content less than F^- 300 micrograms/litre (0.3 parts per million)

- By mouth

Child 6 months–3 years F^- 250 micrograms daily

Child 3–6 years F^- 500 micrograms daily

Child 6 years and over F^- 1 mg daily

Water content between F^- 300 and 700 micrograms/litre (0.3–0.7 parts per million)

Child 3–6 years F^- 250 micrograms daily

Child 6 years and over F^- 500 micrograms daily

Water content above F^- 700 micrograms/litre (0.7 parts per million), supplements not advised

Note These doses reflect the recommendations of the British Dental Association, the British Society of Paediatric Dentistry and the British Association for the Study of Community Dentistry (*Br Dent J* 1997; 182: 6–7)

Tablets

Counselling Tablets should be sucked or dissolved in the mouth and taken preferably in the evening. There are arrangements for health authorities to supply fluoride tablets in the course of pre-school dental schemes, and they may also be supplied in school dental schemes.

En-De-Kay® (Manx)

Fluotabs 3–6 years, orange-flavoured, scored, sodium fluoride 1.1 mg (F^- 500 micrograms), net price 200-tab pack = £2.38

Dental prescribing on NHS May be prescribed as Sodium Fluoride Tablets

Fluotabs 6+ years, orange-flavoured, scored, sodium fluoride 2.2 mg (F^- 1 mg), net price 200-tab pack = £2.38

Dental prescribing on NHS May be prescribed as Sodium Fluoride Tablets

Fluor-a-day® (Dental Health)

Tablets, buff, sodium fluoride 1.1 mg (F^- 500 micrograms), net price 200-tab pack = £2.79; 2.2 mg (F^- 1 mg), 200-tab pack = £2.79

Dental prescribing on NHS May be prescribed as Sodium Fluoride Tablets

■ Oral drops

Note Fluoride supplements not considered necessary below 6 months of age (see notes above)

En-De-Kay® (Manx)

Fluodrops® (= paediatric drops), sugar-free, sodium fluoride 550 micrograms (F^- 250 micrograms)/0.15 mL. Net price 60 mL = £2.38

Dental prescribing on NHS May be prescribed as Sodium Fluoride Oral Drops

■ Mouthwashes

Rinse mouth for 1 minute and spit out

Counselling Avoid eating, drinking, or rinsing mouth for 15 minutes after use

En-De-Kay® (Manx)

Daily fluoride mouthrinse (= mouthwash), blue, sodium fluoride 0.05%. Net price 250 mL = £1.50

Dose

Child 6 years and over for *daily* use, rinse with 10 mL

Dental prescribing on NHS May be prescribed as Sodium Fluoride Mouthwash 0.05%

Fluorinse (= mouthwash), red, sodium fluoride 2%. Net price 100 mL = £4.97. Counselling, see above

Dose

Child 8 years and over for *daily* use, dilute 5 drops to 10 mL of water; for *weekly* use, dilute 20 drops to 10 mL

Dental prescribing on NHS May be prescribed as Sodium Fluoride Mouthwash 2%

FluoridGard® (Colgate-Palmolive)

Daily dental rinse (= mouthwash), blue, sodium fluoride 0.05%. Net price 400 mL = £2.99. Counselling, see above

Dose

Child 6 years and over for *daily* use, rinse with 10 mL

Dental prescribing on NHS May be prescribed as Sodium Fluoride Mouthwash 0.05%

■ Toothpastes**Duraphat®** (Colgate-Palmolive) (PoM)

Duraphat® '2800 ppm' toothpaste, sodium fluoride 0.619%. Net price 75 mL = £3.26. Counselling, see below

Dose

Child over 10 years apply 1 cm twice daily using a toothbrush

Counselling Brush teeth for 1 minute before spitting out. Avoid drinking or rinsing mouth for 30 minutes after use

Dental prescribing on NHS May be prescribed as Sodium Fluoride Toothpaste 0.619%

Duraphat® '5000 ppm' toothpaste, sodium fluoride 1.1%. Net price 51 g = £6.50. Counselling, see below

Dose

Child over 16 years apply 2 cm 3 times daily after meals using a toothbrush

Counselling Brush teeth for 3 minutes before spitting out

Dental prescribing on NHS May be prescribed as Sodium Fluoride Toothpaste 1.1%

9.5.4 Zinc

Zinc supplements should not be given unless there is good evidence of deficiency (hypoproteinaemia spuriously lowers plasma-zinc concentration) or in zinc-losing conditions. Zinc deficiency can occur as a result of inadequate diet or malabsorption; excessive loss of zinc can occur in trauma, burns, and protein-losing conditions. A zinc supplement is given until clinical improvement occurs, but it may need to be continued in severe malabsorption, metabolic disease, or in zinc-losing states. Zinc is used in the treatment of Wilson's disease (section 9.8.1) and acrodermatitis enteropathica, a rare inherited abnormality of zinc absorption.

Parenteral nutrition regimens usually include trace amounts of zinc (section 9.3). If necessary, further zinc can be added to some intravenous feeding regimens.

ZINC SULFATE

Cautions interactions: Appendix 1 (zinc)

Renal impairment accumulation may occur in acute renal failure

Pregnancy crosses placenta; risk theoretically minimal, but no information available

Breast-feeding present in milk; risk theoretically minimal, but no information available

Side-effects abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, gastritis; irritability, headache, lethargy

Licensed use *Solvazinc®* not licensed for use in acrodermatitis enteropathica

Solvazinc® (Galen)

Effervescent tablets, zinc sulfate monohydrate

125 mg (45 mg zinc), net price 30 = £4.32. Label: 13, 21

Dose

Zinc deficiency (see notes above)

● By mouth

Neonate 1 mg/kg elemental zinc daily

Child under 10 kg half a tablet daily in water after food, adjusted as necessary

Child 10–30 kg half a tablet 1–3 times daily in water after food, adjusted as necessary

Child over 30 kg 1 tablet 1–3 times daily in water after food, adjusted as necessary

Acrodermatitis enteropathica

● By mouth

Neonate 0.5–1 mg/kg elemental zinc twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted as necessary

Child 1 month–18 years 0.5–1 mg/kg elemental zinc twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted as necessary

9.6 Vitamins

- 9.6.1 Vitamin A
- 9.6.2 Vitamin B group
- 9.6.3 Vitamin C
- 9.6.4 Vitamin D
- 9.6.5 Vitamin E
- 9.6.6 Vitamin K
- 9.6.7 Multivitamin preparations

Vitamins are used for the prevention and treatment of specific deficiency states or where the diet is known to be inadequate; they may be prescribed in the NHS to prevent or treat deficiency but not as dietary supplements. Except for iron-deficiency anaemia, a primary vitamin or mineral deficiency due to simple dietary inadequacy is rare in the developed world. Some children may be at risk of developing deficiencies because of an inadequate intake, impaired vitamin synthesis or malabsorption in disease states such as cystic fibrosis and Crohn's disease.

The use of vitamins as general 'pick-me-ups' is of unproven value and the 'fad' for mega-vitamin therapy with water-soluble vitamins, such as ascorbic acid and pyridoxine, is unscientific and can be harmful. Many vitamin supplements are described as 'multivitamin' but few contain the whole range of essential vitamins and many contain relatively high amounts of vitamins A and D. Care should be taken to ensure the correct dose is not exceeded.

Dietary reference values for vitamins are available in the Department of Health publication:

Dietary Reference Values for Food Energy and Nutrients for the United Kingdom: Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy. *Report on Health and Social Subjects 41*. London: HMSO, 1991

Dental patients It is unjustifiable to treat stomatitis or glossitis with mixtures of vitamin preparations; this delays diagnosis and correct treatment.

Most patients who develop a nutritional deficiency despite an adequate intake of vitamins have malabsorption and if this is suspected the patient should be referred to a medical practitioner.

9.6.1 Vitamin A

Deficiency of vitamin A (retinol) is associated with ocular defects (particularly xerophthalmia) and an increased susceptibility to infections, but deficiency is rare in the UK (even in disorders of fat absorption).

Vitamin A supplementation may be required in children with liver disease, particularly cholestatic liver disease, due to the malabsorption of fat soluble vitamins. In those with complete biliary obstruction an intramuscular dose once a month may be appropriate.

Treatment is sometimes initiated with very high doses of vitamin A and the child should be monitored closely; very high doses are associated with acute toxicity.

Preterm neonates have low plasma concentrations of vitamin A and are usually given vitamin A supplements, often as part of an oral multivitamin preparation (section 9.6.7) once enteral feeding has been established.

Massive overdose can cause rough skin, dry hair, an enlarged liver, and a raised erythrocyte sedimentation rate and raised serum calcium and serum alkaline phosphatase concentrations.

Pregnancy In view of evidence suggesting that high levels of vitamin A may cause birth defects, women who are (or may become) pregnant are advised not to take vitamin A supplements (including tablets and fish-liver oil drops), except on the advice of a doctor or an antenatal clinic; nor should they eat liver or products such as liver pâté or liver sausage.

VITAMIN A (Retinol)

Cautions see notes above; **interactions:** Appendix 1 (vitamins)

Pregnancy excessive doses can be teratogenic; see also notes above

Breast-feeding toxicity likely if mother taking high doses

Side-effects see notes above

Licensed use preparations containing only vitamin A are not licensed

Indications and dose

See also notes above

Vitamin A deficiency

• By mouth

Neonate 5000 units daily

Child 1 month–1 year 5000 units daily with or after food

Child 1–18 years 10 000 units daily with or after food

Note Higher doses may be used initially for treatment of severe deficiency

Prevention of deficiency in complete biliary obstruction

• By intramuscular injection

Neonate 50 000 units once a month

Child 1 month–1 year 50 000 units once a month

Arovit® (Non-proprietary)

Oral solution, vitamin A 150 000 units/mL (1 drop contains approx. 5000 units)

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Aquasol-A® (Non-proprietary)

Injection, vitamin A (as palmitate) 50 000 units/mL, 2-mL amp

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

VITAMINS A and D

Cautions see notes above and section 9.6.4; prolonged excessive ingestion of vitamins A and D can lead to hypervitaminosis; **interactions:** Appendix 1 (vitamins)

Pregnancy see notes above

Side-effects see notes above and section 9.6.4

Licensed use not licensed in children under 6 months of age

Indications and dose

See notes above and section 9.6.4

Prevention of vitamin A and D deficiency see individual preparations for dose information

■ Vitamins A and D

Vitamins A and D (Non-proprietary)

Capsules, vitamin A 4000 units, vitamin D 400 units (10 micrograms). Net price 84 = £8.42

Note May be difficult to obtain

Dose

Child 1–18 years 1 capsule daily

■ Vitamins A, C and D

Healthy Start Children's Vitamin Drops (Non-proprietary)

Oral drops, vitamin A 5000 units, vitamin D 2000 units (50 micrograms), ascorbic acid 150 mg/mL

Available free of charge to children under 4 years in families on the Healthy Start Scheme, or alternatively may be available direct to the public—further information for healthcare professionals can be accessed at www.healthystart.nhs.uk.

Beneficiaries can contact their midwife or health visitor for further information on where to obtain supplies.

Dose

Prevention of vitamin deficiency

• By mouth

Child 1 month–5 years 5 drops daily (5 drops contain vitamin A approx. 700 units, vitamin D approx. 300 units (7.5 micrograms), ascorbic acid approx. 20 mg)

Note *Healthy Start Vitamins for women* (containing ascorbic acid, vitamin D, and folic acid) are also available free of charge to women on the Healthy Start Scheme during pregnancy and until their baby is one year old, or alternatively may be available direct to the public—further information for healthcare professionals can be accessed at www.healthystart.nhs.uk. Beneficiaries can contact their midwife or health visitor for further information on where to obtain supplies.

9.6.2 Vitamin B group

Deficiency of the B vitamins, other than vitamin B₁₂ (section 9.1.2), is rare in the UK and is usually treated by preparations containing thiamine (B₁), and riboflavin (B₂). Other members (or substances traditionally classified as members) of the vitamin B complex such as aminobenzoic acid, biotin, choline, inositol, and pantothenic acid or panthenol may be included in vitamin B preparations, but there is no evidence of their value as supplements; however, they can be used in the management of certain metabolic disorders (section 9.8.1). Anaphylaxis has been reported with parenteral B vitamins (see MHRA/CHM advice, below).

As with other vitamins of the B group, pyridoxine (B₆) deficiency is rare, but it may occur during isoniazid therapy (section 5.1.9) or penicillamine treatment in Wilson's disease (section 9.8.1) and is characterised by peripheral neuritis. High doses of **pyridoxine** are given in some metabolic disorders, such as hyperoxaluria, cystathioninuria and homocystinuria; folic acid supplementation may also be beneficial in these disorders (section 9.1.2). Pyridoxine is also used in sideroblastic anaemia (section 9.1.3). Rarely, seizures in the neonatal period or during infancy respond to pyridoxine treatment; pyridoxine should be tried in all cases of early-onset intractable seizures and status epilepticus. Pyridoxine has been tried for a wide variety of other disorders, but there is little sound evidence to support the claims of efficacy, and overdosage induces toxic effects.

A number of mitochondrial disorders may respond to treatment with certain B vitamins but these disorders

require specialist management. **Thiamine** is used in the treatment of maple syrup urine disease, mitochondrial respiratory chain defects and, together with riboflavin, in the treatment of congenital lactic acidosis; riboflavin is also used in glutaric acidurias and cytochrome oxidase deficiencies; biotin (section 9.8.1) is used in carboxylase defects.

Folic acid and vitamin B₁₂ are used in the treatment of megaloblastic anaemia (section 9.1.2). Folinic acid (available as calcium folinate) is used in association with cytotoxic therapy (section 8.1).

RIBOFLAVIN

(Riboflavin, vitamin B₂)

Cautions see notes above

Pregnancy crosses the placenta but no adverse effects reported, information at high doses limited

Breast-feeding present in breast milk but no adverse effects reported, information at high doses limited

Side-effects bright yellow urine

Licensed use not licensed in children

Indications and dose

See also notes above

Metabolic diseases

• By mouth

Neonate 50 mg 1–2 times daily, adjusted according to response

Child 1 month–18 years 50–100 mg 1–2 times daily, adjusted according to response, up to 400 mg daily has been used

Riboflavin (Non-proprietary)

Tablets, 10 mg, 50 mg and 100 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

■ Oral vitamin B complex preparations

See below

THIAMINE

(Vitamin B₁)

Cautions anaphylactic shock may occasionally follow injection (see MHRA/CHM advice below)

MHRA/CHM advice (September 2007)

Although potentially serious allergic adverse reactions may rarely occur during, or shortly after, parenteral administration, the CHM has recommended that:

1. This should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of Wernicke-Korsakoff syndrome where treatment with thiamine is essential;
2. Intravenous administration should be by infusion over 30 minutes;
3. Facilities for treating anaphylaxis (including resuscitation facilities) should be available when parenteral thiamine is administered.

Breast-feeding severely thiamine-deficient mothers should avoid breast-feeding as toxic methyl-glyoxal present in milk

Side-effects hypersensitivity reactions to injection

Licensed use not licensed in children

Indications and dose

See also notes above

Maple syrup urine disease

- By mouth

Neonate 5 mg/kg daily, adjusted as necessary**Child 1 month–18 years** 5 mg/kg daily, adjusted as necessary**Metabolic disorders including congenital lactic acidosis**

- By mouth or by intravenous infusion over 30 minutes

Neonate 50–200 mg once daily (total dose may alternatively be given in 2–3 divided doses), adjusted as necessary**Child 1 month–18 years** 100–300 mg once daily (total dose may alternatively be given in 2–3 divided doses), adjusted as necessary; up to 2 g daily may be necessary**Thiamine** (Non-proprietary)

Tablets, thiamine hydrochloride 50 mg, net price 100 = £3.85; 100 mg, 100 = £5.98

Brands include Benerva® 

Injection, 50 mg/mL, 2-mL vial; 100 mg/mL, 2-mL vial

Injection (intramuscular), 100 mg/mL, 5-mL vial
Available from 'special-order' manufacturers or specialist importing companies, see p. 840**Note** Some preparations may contain phenol as a preservative**Oral vitamin B complex preparations**

See below

PYRIDOXINE HYDROCHLORIDE
(Vitamin B₆)**Cautions** see notes above; risk of cardiovascular collapse with intravenous injection—resuscitation facilities must be available, monitor closely; **interactions:** Appendix 1 (vitamins)**Side-effects** sensory neuropathy reported with high doses given for extended periods**Licensed use** not licensed for use in children**Indications and dose**

See also notes above

Metabolic diseases including cystathioninuria and homocystinuria

- By mouth

Neonate 50–100 mg 1–2 times daily**Child 1 month–18 years** 50–250 mg 1–2 times daily**Treatment of isoniazid-induced neuropathy**

- By mouth

Neonate 5–10 mg daily**Child 1 month–12 years** 10–20 mg 2–3 times daily**Child 12–18 years** 30–50 mg 2–3 times daily**Prevention of isoniazid-induced neuropathy**

- By mouth

Neonate 5 mg daily**Child 1 month–12 years** 5–10 mg daily**Child 12–18 years** 10 mg daily**Prevention of penicillamine-induced neuropathy in Wilson's disease (see notes above)**

- By mouth

Child 1–12 years 5–10 mg daily**Child 12–18 years** 10 mg daily**Pyridoxine-dependent seizures**

- By intravenous injection or by mouth

Neonate initial test dose 50–100 mg by intravenous injection, may be repeated; if responsive followed by an oral maintenance dose of 50–100 mg once daily, adjusted as necessary**Child 1 month–12 years** initial test dose 50–100 mg daily; if responsive followed by an oral dose of 20–50 mg 1–2 times daily, adjusted as necessary; doses up to 30 mg/kg or 1 g daily have been used**Pyridoxine** (Non-proprietary)

Tablets, pyridoxine hydrochloride 10 mg, net price 500 = £8.48; 20 mg, 500 = £8.53; 50 mg, 28 = £3.29

Injection, 25 mg/mL, 2 mL vial

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Oral vitamin B complex preparations**Note** Other multivitamin preparations are in section 9.6.7.**Vitamin B Tablets, Compound** 

Tablets, nicotinamide 15 mg, riboflavin 1 mg, thiamine hydrochloride 1 mg, net price 28 = £22.26

Vitamin B Tablets, Compound, Strong 

Tablets, brown, f/c or s/c, nicotinamide 20 mg, pyridoxine hydrochloride 2 mg, riboflavin 2 mg, thiamine hydrochloride 5 mg. Net price 28-tab pack = £2.03

Vigranon B® (Wallace Mfg) **Syrup**, thiamine hydrochloride 5 mg, riboflavin 2 mg, nicotinamide 20 mg, pyridoxine hydrochloride 2 mg, panthanol 3 mg/5 mL. Net price 150 mL = £2.41**Dose****Treatment of deficiency**

- By mouth

Child 1 month–1 year 5 mL 3 times daily**Child 1–12 years** 10 mL 3 times daily**Child 12–18 years** 10–15 mL 3 times daily**Prophylaxis of deficiency**

- By mouth

Child 1 month–1 year 5 mL once daily**Child 1–12 years** 5 mL twice daily**Child 12–18 years** 5 mL 3 times daily**9.6.3 Vitamin C**
(Ascorbic acid)

Vitamin C therapy is essential in scurvy, but less florid manifestations of vitamin C deficiency have been reported. Vitamin C is used to enhance the excretion of iron one month after starting desferrioxamine therapy (section 9.1.3); it is given separately from food as it also enhances iron absorption. Vitamin C is also used in the treatment of some inherited metabolic disorders, particularly mitochondrial disorders; specialist management of these conditions is required.

Severe scurvy causes gingival swelling and bleeding margins as well as petechiae on the skin. This is, however, exceedingly rare and a child with these signs is more likely to have leukaemia. Investigation should not be delayed by a trial period of vitamin treatment.

Claims that vitamin C ameliorates colds or promotes wound healing have not been proved.

ASCORBIC ACID

(Vitamin C)

Cautions interactions: Appendix 1 (vitamins)

Contra-indications hyperoxaluria

Side-effects nausea, diarrhoea; headache, fatigue; hyperoxaluria

Licensed use not licensed for metabolic disorders

Indications and dose

Treatment of scurvy

• By mouth

Child 1 month–4 years 125–250 mg daily in 1–2 divided doses

Child 4–12 years 250–500 mg daily in 1–2 divided doses

Child 12–18 years 500 mg–1 g daily in 1–2 divided doses

Adjunct to desferrioxamine (see notes above)

• By mouth

Child 1 month–18 years 100–200 mg daily 1 hour before food

Metabolic disorders (tyrosinaemia type III; transient tyrosinaemia of the newborn; glutathione synthase deficiency; Hawkinsinuria)

• By mouth

Neonate 50–200 mg daily, adjusted as necessary

Child 1 month–18 years 200–400 mg daily in 1–2 divided doses, adjusted as necessary; up to 1 g daily may be required

Ascorbic Acid (Non-proprietary)

Tablets, ascorbic acid 50 mg, net price 28 = £2.13; 100 mg, 28 = £2.41; 200 mg, 28 = £3.14; 500 mg (label: 24), 28 = £4.54

Excipients may include aspartame

Brands include Redoxon®

Injection, ascorbic acid 100 mg/mL, net price 5-mL amp = £4.39

Excipients include metabisulfite

9.6.4 Vitamin D

Note The term Vitamin D is used for a range of compounds including ergocalciferol (calciferol, vitamin D₂), colecalciferol (vitamin D₃), dihydrotachysterol, alfalcidol (12-hydroxycholecalciferol), and calcitriol (1,25-dihydroxycholecalciferol).

Asymptomatic vitamin D deficiency is common in the United Kingdom; symptomatic deficiency may occur in certain ethnic groups, particularly as rickets or hypocalcaemia, and rarely in association with malabsorption. The amount of vitamin D required in infancy is related to the stores built up *in-utero* and subsequent exposure to sunlight. The amount of vitamin D in breast milk varies and some breast-fed babies, particularly if pre-term or born to vitamin D deficient mothers, may

become deficient. Most formula milk and supplement feeds contain adequate vitamin D to prevent deficiency.

Simple, nutritional vitamin D deficiency can be prevented by oral supplementation of 10 micrograms (400 units) of **ergocalciferol** (calciferol, vitamin D₂) or **colecalciferol** (vitamin D₃) daily, using multi-vitamin drops (section 9.6.7), preparations of vitamins A and D (section 9.6.1), manufactured 'special' solutions, or as calcium and ergocalciferol tablets (although the calcium and other vitamins in supplements are unnecessary); excessive supplementation may cause hypercalcaemia.

Inadequate bone mineralisation can be caused by a deficiency, or a lack of action of vitamin D or its active metabolite. In childhood this causes bowing and distortion of bones (rickets). In nutritional vitamin D deficiency rickets, initial high doses of ergocalciferol or colecalciferol should be reduced to supplemental doses after 8–12 weeks, as there is a significant risk of hypercalcaemia (see caution below). However, calcium supplements are recommended if there is hypocalcaemia or evidence of a poor dietary calcium intake. A single large dose of ergocalciferol or colecalciferol can also be effective for the treatment of nutritional vitamin D deficiency rickets.

Poor bone mineralisation in neonates and young children may also be due to inadequate intake of phosphate or calcium particularly during long-term parenteral nutrition—supplementation with phosphate (section 9.5.2.1) or calcium (section 9.5.1.1) may be required.

Hypophosphataemic rickets occurs due to abnormal phosphate excretion; treatment with high doses of oral phosphate (section 9.5.2.1), and hydroxylated (activated) forms of vitamin D allow bone mineralisation and optimise growth.

Nutritional deficiency of vitamin D is best treated with colecalciferol or ergocalciferol. Preparations containing calcium and colecalciferol are also occasionally used in children where there is evidence of combined calcium and vitamin D deficiency. Vitamin D deficiency caused by *intestinal malabsorption* or *chronic liver disease* usually requires vitamin D in pharmacological doses, such as **ergocalciferol** in doses of up to 40 000 units daily; the hypocalcaemia of *hypoparathyroidism* often requires higher doses in order to achieve normocalcaemia and alfalcidol is generally preferred.

Vitamin D supplementation is often given in combination with calcium supplements for persistent hypocalcaemia in neonates, and in chronic renal disease.

Vitamin D requires hydroxylation, by the kidney and liver, to its active form therefore the hydroxylated derivatives **alfalcidol** or **calcitriol** should be prescribed if patients with *severe liver* or *renal impairment* require vitamin D therapy. Alfalcidol is generally preferred in children as there is more experience of its use and appropriate formulations are available. Calcitriol is unlicensed for use in children and is generally reserved for those with severe liver disease.

Important. All patients receiving pharmacological doses of vitamin D or its analogues should have their plasma-calcium concentration checked at intervals (initially once or twice weekly) and whenever nausea or vomiting occur.

ERGOCALCIFEROL(Calciferol, Vitamin D₂)

Cautions see notes above; monitor plasma-calcium concentration in patients receiving high doses and in renal impairment; **interactions:** Appendix 1 (vitamins)

Contra-indications hypercalcaemia; metastatic calcification

Pregnancy high doses teratogenic in *animals* but therapeutic doses unlikely to be harmful

Breast-feeding caution with high doses as may cause hypercalcaemia in infant—monitor serum-calcium concentration

Side-effects symptoms of overdosage include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine

Licensed use Calcium and Ergocalciferol tablets not licensed for use in children under 6 years

Indications and dose

See also notes above

Nutritional vitamin-D deficiency rickets

• By mouth

Child 1–6 months 3000 units daily, adjusted as necessary

Child 6 months–12 years 6000 units daily, adjusted as necessary

Child 12–18 years 10 000 units daily, adjusted as necessary

Nutritional or physiological supplement; prevention of rickets

• By mouth

Neonate 400 units daily

Child 1 month–18 years 400–600 units daily

Vitamin D deficiency in intestinal malabsorption or in chronic liver disease

• By mouth or by intramuscular injection

Child 1–12 years 10 000–25 000 units daily, adjusted as necessary

Child 12–18 years 10 000–40 000 units daily, adjusted as necessary

Pharmacological strengths

(see notes above)

The BP directs that when calciferol is prescribed or demanded, colecalciferol or ergocalciferol should be dispensed or supplied

Ergocalciferol (Non-proprietary)

Tablets, ergocalciferol 100 micrograms (10 000 units), net price 100 = £21.99; 1.25 mg (50 000 units), 100 = £30.34

Note May be difficult to obtain

Important When the strength of the tablets ordered or prescribed is not clear, the intention of the prescriber or purchaser with respect to the strength (expressed in micrograms or milligrams per tablet) should be ascertained.

Injection, ergocalciferol, 7.5 mg (300 000 units)/mL in oil, net price 1-mL amp = £8.50, 2-mL amp = £9.85

Note Other formulations of ergocalciferol are available from 'special-order' manufacturers or specialist importing companies, see p. 840

Daily supplements

Note There is no plain vitamin D tablet available for treating simple deficiency (see notes above). Alternatives include vitamins capsules (section 9.6.7), preparations of vitamins A and D (section 9.6.1), and calcium and ergocalciferol tablets (see below).

For prescribing information on calcium, see section 9.5.1

Calcium and Ergocalciferol (Non-proprietary)

(Calcium and Vitamin D)

Tablets, calcium lactate 300 mg, calcium phosphate 150 mg (calcium 97 mg or Ca²⁺ 2.4 mmol), ergocalciferol 10 micrograms (400 units). Net price 28-tab pack = £10.88. Counselling, crush before administration or may be chewed

ALFACALCIDOL(1 α -Hydroxycholecalciferol)

Cautions see under Ergocalciferol; also nephrolithiasis

Contra-indications see under Ergocalciferol

Pregnancy see under Ergocalciferol

Breast-feeding see under Ergocalciferol

Side-effects see under Ergocalciferol; also *rarely* nephrocalcinosis, pruritus, rash, and urticaria

Indications and dose

See also notes above

Hypophosphataemic rickets; persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism

• By mouth or by intravenous injection

Child 1 month–12 years 25–50 nanograms/kg (max. 1 microgram) once daily, adjusted as necessary

Child 12–18 years 1 microgram once daily, adjusted as necessary

Persistent neonatal hypocalcaemia

• By mouth or by intravenous injection

Neonate 50–100 nanograms/kg once daily, adjusted as necessary (up to 2 micrograms/kg daily may be needed in resistant cases)

Prevention of vitamin D deficiency in renal or cholestatic liver disease

• By mouth or by intravenous injection

Neonate 20 nanograms/kg once daily, adjusted as necessary

Child 1 month–12 years, body-weight under 20 kg 15–30 nanograms/kg (max. 500 nanograms) once daily; **body-weight over 20 kg** 250–500 nanograms once daily, adjusted as necessary

Child 12–18 years 250–500 nanograms once daily, adjusted as necessary

Alfacalcidol (Non-proprietary) **[PoM]**

Capsules, alfacalcidol 250 nanograms, net price 30-cap pack = £2.62; 500 nanograms 30-cap pack = £5.77; 1 microgram 30-cap pack = £5.89

One-Alpha[®] (LEO) **[PoM]**

Capsules, alfacalcidol 250 nanograms (white), net price 30-cap pack = £3.37; 500 nanograms (red), 30-cap pack = £6.27; 1 microgram (brown), 30-cap pack = £8.75

Excipients include sesame oil

Oral drops, sugar-free, alfacalcidol 2 micrograms/mL (1 drop contains approx. 100 nanograms), net price 10 mL = £21.30

Excipients include alcohol

Note The concentration of alfacalcidol in *One-Alpha® drops* is 10 times greater than that of the former preparation *One-Alpha® solution*.

Injection, alfacalcidol 2 micrograms/mL, net price 0.5-mL amp = £2.16, 1-mL amp = £4.11

Excipients include alcohol, propylene glycol (caution in neonates, see, p. 2)

Note Shake ampoule for at least 5 seconds before use

CALCITRIOL

(1,25-Dihydroxycholecalciferol)

Cautions see under Ergocalciferol; monitor plasma calcium, phosphate, and creatinine during dosage titration

Contra-indications see under Ergocalciferol

Pregnancy see under Ergocalciferol

Breast-feeding see under Ergocalciferol

Side-effects see under Ergocalciferol

Licensed use not licensed for use in children

Indications and dose

See also notes above

Vitamin D dependent rickets; hypophosphataemic rickets; persistent hypocalcaemia due to hypoparathyroidism or pseudo-hypoparathyroidism (limited experience)

• By mouth

Child 1 month–12 years initially 15 nanograms/kg (max. 250 nanograms) once daily, increased if necessary in steps of 5 nanograms/kg daily (max. 250 nanograms) every 2–4 weeks

Child 12–18 years initially 250 nanograms once daily increased if necessary in steps of 5 nanograms/kg daily (max. 250 nanograms step) every 2–4 weeks; usual dose 0.5–1 microgram daily

Administration Contents of capsule may be administered by oral syringe

Calcitriol (Non-proprietary) **[PoM]**

Capsules, calcitriol 250 nanograms, net price 30-cap pack = £5.41, 100-cap pack = £19.15; 500 nanograms, 30-cap pack = £9.68, 100-cap pack = £25.76

Rocaltrol® (Roche) **[PoM]**

Capsules, calcitriol 250 nanograms (red/white), net price 100 = £18.04; 500 nanograms (red), 100 = £32.25

COLECALCIFEROL

(Cholecalciferol, vitamin D₃)

Cautions see under Ergocalciferol

Contra-indications see under Ergocalciferol

Pregnancy see under Ergocalciferol

Breast-feeding see under Ergocalciferol

Side-effects see under Ergocalciferol

Licensed use *Adcal-D3®*, *Calceos®*, and *Fultium-D₃®* not licensed for use in children under 12 years; *Calcit®D₃*, *Calcichew-D₃® Forte*, *Calcichew-D₃® 500 mg/400 unit*, and *Kalcipos-D®* not licensed for use in children (age range not specified by manufacturers); *Accrete D3®*, *Calfovit D3®*, and *Natecal D3®* not licensed for use in children under 18 years

Indications and dose

See under Ergocalciferol and notes above—alternative to Ergocalciferol, see also Pharmacological Strengths

Fultium-D₃® (Internis) **[PoM]**

Capsules, colecalciferol 20 micrograms (800 units), net price 30-cap pack = £3.60, 90-cap pack = £10.80. Label: 25

Excipients include arachis (peanut) oil

Colecalciferol

Various formulations available from 'special-order' manufacturers or specialist importing companies, see p. 840

With calcium

For prescribing information on calcium, see section 9.5.1

Accrete D3® (Internis)

Tablets, f/c, calcium carbonate 1.5 g (calcium 600 mg or Ca²⁺ 15 mmol), colecalciferol 10 micrograms (400 units), net price 60-tab pack = £2.95

Adcal-D₃® (ProStrakan)

Tablets (chewable), lemon or tutti-frutti flavour, calcium carbonate 1.5 g (calcium 600 mg or Ca²⁺ 15 mmol), colecalciferol 10 micrograms (400 units), net price 56-tab pack = £3.65, 112-tab pack = £7.49. Label: 24

Dissolve (effervescent tablets), lemon flavour, calcium carbonate 1.5 g (calcium 600 mg or Ca²⁺ 15 mmol), colecalciferol 10 micrograms (400 units), net price 56-tab pack = £5.99. Label: 13

Caplets (=tablets), f/c, calcium carbonate 750 mg (calcium 300 mg or Ca²⁺ 7.5 mmol), colecalciferol 5 micrograms (200 units), net price 112-tab pack = £3.65

Cacit® D3 (Warner Chilcott)

Granules, effervescent, lemon flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca²⁺ 12.5 mmol), colecalciferol 11 micrograms (440 units)/sachet, net price 30-sachet pack = £4.06. Label: 13

Calceos® (Galen)

Tablets (chewable), lemon flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca²⁺ 12.5 mmol), colecalciferol 10 micrograms (400 units), net price 60-tab pack = £3.58. Label: 24

Calcichew-D₃® (Takeda)

Calcichew-D₃® tablets (chewable), orange flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca²⁺ 12.5 mmol), colecalciferol 5 micrograms (200 units), net price 100-tab pack = £7.68. Label: 24

Excipients include aspartame (section 9.4.1)

Calcichew-D₃® Forte tablets (chewable), lemon flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca²⁺ 12.5 mmol), colecalciferol 10 micrograms (400 units), net price 100-tab pack = £7.08. Label: 24

Excipients include aspartame (section 9.4.1)

Calcichew-D₃® 500 mg/400 unit caplets, f/c, lemon flavour, calcium carbonate providing calcium 500 mg (Ca²⁺ 12.5 mmol), colecalciferol 10 micrograms (400 units), net price 100-tab pack = £7.43

Excipients include propylene glycol (see Excipients, p. 2)

Calfovite D3® (Menarini)

Powder, lemon flavour, calcium phosphate 3.1 g (calcium 1.2 g or Ca^{2+} 30 mmol), colecalciferol 20 micrograms (800 units), net price 30-sachet pack = £4.32. Label: 13, 21

Kalcipos-D® (Meda) (PoM)

Tablets (chewable), calcium carbonate providing calcium 500 mg (Ca^{2+} 12.5 mmol), colecalciferol 20 micrograms (800 units), net price 30-tab pack = £4.21. Label: 24

Natocal D3® (Chiesi)

Tablets (chewable), (aniseed, peppermint, and molasses flavour), calcium carbonate 1.5 g (calcium 600 mg or Ca^{2+} 15 mmol), colecalciferol 10 micrograms (400 units), net price 60-tab pack = £3.63. Label: 24

Excipients include aspartame (section 9.4.1)

9.6.5 Vitamin E (Tocopherols)

The daily requirement of vitamin E has not been well defined. Vitamin E supplements are given to children with fat malabsorption such as in cystic fibrosis and cholestatic liver disease. In children with abetalipoproteinaemia abnormally low vitamin E concentrations may occur in association with neuromuscular problems; this usually responds to high doses of vitamin E. Some neonatal units still administer a single intramuscular dose of vitamin E at birth to preterm neonates to reduce the risk of complications; no trials of long-term outcome have been carried out. The intramuscular route should also be considered in children with severe liver disease when response to oral therapy is inadequate.

Vitamin E has been tried for various other conditions but there is little scientific evidence of its value.

ALPHA TOCOPHERYL ACETATE

Cautions predisposition to thrombosis; increased risk of necrotising enterocolitis in preterm neonates (see administration); **interactions:** Appendix 1 (vitamins)

Pregnancy no evidence of safety of high doses

Breast-feeding excreted in milk, minimal risk although caution with large doses

Side-effects diarrhoea and abdominal pain, particularly with high doses

Indications and dose**Vitamin E deficiency**

- By mouth

Neonate 10 mg/kg once daily

Child 1 month–18 years 2–10 mg/kg daily, up to 20 mg/kg has been used

Malabsorption in cystic fibrosis

- By mouth (with food and pancreatic enzymes)

Child 1 month–1 year 50 mg once daily, adjusted as necessary

Child 1–12 years 100 mg once daily, adjusted as necessary

Child 12–18 years 100–200 mg once daily, adjusted as necessary

Vitamin E deficiency in cholestasis and severe liver disease

- By mouth

Neonate 10 mg/kg daily

Child 1 month–12 years initially 100 mg daily, adjusted according to response; up to 200 mg/kg daily may be required

Child 12–18 years initially 200 mg daily, adjusted according to response; up to 200 mg/kg daily may be required

- By intramuscular injection

Neonate 10 mg/kg once a month

Child 1 month–18 years 10 mg/kg (max. 100 mg) once a month

Malabsorption in abetalipoproteinaemia

- By mouth

Neonate 100 mg/kg once daily

Child 1 month–18 years 50–100 mg/kg once daily

Vitamin E Suspension (Non-proprietary)

Suspension, alpha tocopheryl acetate 100 mg/mL.

Net price 100 mL = £42.12

Excipients include sucrose

Administration consider dilution in neonates due to high osmolality (see Cautions)

Note Tablets containing tocopheryl acetate are available from 'special-order' manufacturers or specialist importing companies, see p. 840

Vitamin E Injection

Injection tocopheryl acetate 50 mg/mL, 2-mL ampoule

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

ALPHA TOCOPHEROL

Cautions predisposition to thrombosis; **interactions:** Appendix 1 (vitamins)

Contra-indications preterm neonates

Hepatic impairment manufacturer advises caution and monitor closely—no information available

Renal impairment manufacturer advises caution and monitor closely; risk of renal toxicity due to polyethylene glycol content

Pregnancy manufacturer advises caution; no evidence of harm in animal studies

Breast-feeding manufacturer advises use only if potential benefit outweighs risk—no information available

Side-effects diarrhoea; *less commonly* asthenia, headache, pruritus, disturbances in serum-potassium and serum-sodium concentrations, alopecia, and rash

Vedrop® (Orphan Europe) ▼ (PoM)

Oral solution, yellow, D-alpha tocopherol (as tocopherol) 50 mg/mL, net price 20 mL = £54.55, 60 mL = £163.65 (all with oral syringe)

Note Tocopherol is a water-soluble form of D-alpha tocopherol

Dose

Vitamin E deficiency because of malabsorption in congenital or hereditary chronic cholestasis

- By mouth

Neonate 17 mg/kg daily, adjusted as necessary

Child 1 month–18 years 17 mg/kg daily, adjusted as necessary

9.6.6 Vitamin K

Vitamin K is necessary for the production of blood clotting factors and proteins necessary for the normal calcification of bone.

Because vitamin K is fat soluble, children with fat malabsorption, especially in biliary obstruction or hepatic disease, may become deficient. For oral administration to prevent vitamin K deficiency in malabsorption syndromes, a water-soluble synthetic vitamin K derivative, **menadiol sodium phosphate** (see Contra-indications below) can be used if supplementation with phytomenadione by mouth has been insufficient.

Oral coumarin anticoagulants act by interfering with vitamin K metabolism in the hepatic cells and their effects can be antagonised by giving vitamin K; for advice on the use of vitamin K in haemorrhage, see section 2.8.2.

Vitamin K deficiency bleeding Neonates are relatively deficient in vitamin K and those who do not receive supplements are at risk of serious bleeding, including intracranial bleeding. The Chief Medical Officer and the Chief Nursing Officer have recommended that all newborn babies should receive vitamin K to prevent vitamin K deficiency bleeding (previously termed haemorrhagic disease of the newborn). Local protocols may vary and an appropriate regimen should be selected after discussion with parents in the antenatal period.

Vitamin K (as phytomenadione) 1 mg may be given by a single intramuscular injection at birth; this prevents vitamin K deficiency bleeding in virtually all babies; preterm neonates may be given 400 micrograms/kg (max. 1 mg). The intravenous route may be used in preterm neonates of very low birth-weight if intramuscular injection is not possible; however, it may not provide the prolonged protection of the intramuscular injection; any babies receiving intravenous vitamin K should be given subsequent oral doses.

Alternatively, in healthy babies who are not at particular risk of bleeding disorders, vitamin K may be given by mouth, and arrangements must be in place to ensure the appropriate regimen is followed. Two doses of a colloidal (mixed micelle) preparation of phytomenadione 2 mg should be given in the first week, the first dose being given at birth and the second at 4–7 days. For exclusively breast-fed babies, a third dose of phytomenadione 2 mg is given at 1 month of age; the third dose is omitted in formula-fed babies because formula feeds contain adequate vitamin K. An alternative regimen is to give one dose of phytomenadione 1 mg by mouth at birth (using the contents of a phytomenadione capsule, see preparation below) to protect from the risk of vitamin K deficiency bleeding in the first week; for exclusively breast-fed babies, further doses of phytomenadione 1 mg are given by mouth (using the contents of a phytomenadione capsule) at weekly intervals for 12 weeks.

For the *treatment* of vitamin K deficiency bleeding, intravenous phytomenadione is used, see Phytomenadione below.

MENADIOL SODIUM PHOSPHATE

Cautions G6PD deficiency (section 9.1.5) and vitamin E deficiency (risk of haemolysis); **interactions:** Appendix 1 (vitamins)

Contra-indications neonates and infants

Pregnancy avoid in late pregnancy and labour unless benefit outweighs risk of neonatal haemolytic anaemia, hyperbilirubinaemia, and kernicterus in neonate

Indications and dose

See notes above

Supplementation in vitamin K malabsorption

• By mouth

Child 1–12 years 5–10 mg daily, adjusted as necessary

Child 12–18 years 10–20 mg daily, adjusted as necessary

Menadiol Phosphate (Non-proprietary)

Tablets, menadiol sodium phosphate equivalent to 10 mg of menadiol phosphate, net price 100-tab pack = £122.48

PHYTOMENADIONE

(Vitamin K₁)

Cautions intravenous injections should be given very slowly—risk of vascular collapse (see also below); **interactions:** Appendix 1 (vitamins)

Pregnancy use if potential benefit outweighs risk

Breast-feeding present in milk, but see notes above

Indications and dose

Neonatal prophylaxis of vitamin-K deficiency bleeding see notes above

Neonatal hypoprothrombinaemia or vitamin-K deficiency bleeding

• By intravenous injection

Neonate 1 mg repeated 8 hourly if necessary

Neonatal biliary atresia and liver disease

• By mouth

Neonate 1 mg daily

Reversal of coumarin anticoagulation when continued anticoagulation required or if no significant bleeding (see also section 2.8.2)—seek specialist advice

• By intravenous injection

Child 1 month–18 years 15–30 micrograms/kg (max. 1 mg) as a single dose, repeated as necessary

Reversal of coumarin anticoagulation when anticoagulation not required or if significant bleeding; treatment of haemorrhage associated with vitamin-K deficiency (see also section 2.8.2)—seek specialist advice

• By intravenous injection

Child 1 month–18 years 250–300 micrograms/kg (max. 10 mg) as a single dose

Neokay® (Neoceuticals) (PoM)

Capsules, brown, phytomenadione 1 mg in an oily basis, net price 12-cap pack = £3.95; 100-cap pack = £34.00

Note The contents of one capsule should be administered by cutting the narrow tubular tip off and squeezing the liquid contents into the mouth; if the baby spits out the dose or is sick within three hours of administration a replacement dose should be given

Dose

Neonatal prophylaxis of vitamin-K deficiency bleeding see notes above

Colloidal formulation

Konakion[®] MM (Roche) (PoM)

Injection, phytomenadione 10 mg/mL in a mixed micelles vehicle. Net price 1-mL amp = 38p

Excipients include glycocholic acid 54.6 mg/amp, lecithin

Cautions reduce dose in liver impairment (glycocholic acid may displace bilirubin); reports of anaphylactoid reactions

Administration Konakion[®] MM may be administered by slow intravenous injection or by intravenous infusion in glucose 5%; **not** for intramuscular injection

Konakion[®] MM Paediatric (Roche) (PoM)

Injection, phytomenadione 10 mg/mL in a mixed micelles vehicle, net price 0.2-mL amp = 94p

Excipients include glycocholic acid 10.9 mg/amp, lecithin

Cautions parenteral administration in premature infants body-weight less than 2.5 kg (increased risk of kernicterus)

Administration Konakion[®] MM Paediatric may be administered by mouth or by intramuscular injection or by intravenous injection. For intravenous injection, may be diluted with Glucose 5% if necessary

Dose

Prevention of deficiency

• By mouth

Preterm neonate 0.6 mL daily

Neonate 0.3 mL daily

Child 1 month–1 year 0.3 mL daily

Child 1–18 years 0.6 mL daily

Cystic fibrosis: prevention of deficiency

• By mouth

Child 1 month–1 year 0.6 mL daily

Child 1–18 years 1.2 mL daily

Dalivit[®] (LPC)

Oral drops, vitamins A, B group, C, and D, net price 25 mL = £3.28, 50 mL = £5.58

Note Contains 5000 units of vitamin A (as palmitate) per 0.6 mL dose

Excipients include sucrose

Dose

Prevention of deficiency

• By mouth

Neonate (including preterm) 0.3 mL daily

Child 1 month–1 year 0.3 mL daily

Child 1–18 years 0.6 mL daily

Cystic fibrosis: prevention of deficiency

• By mouth

Child 1 month–1 year 0.6 mL daily

Child 1–18 years 1 mL daily

9.6.7 Multivitamin preparations

Multivitamin supplements are used in children with vitamin deficiencies and also in malabsorption conditions such as cystic fibrosis or liver disease. To avoid potential toxicity, the content of all vitamin preparations, particularly vitamin A, should be considered when used together with other supplements. Supplementation is not required if nutrient enriched feeds are used; consult a dietician for further advice.

MULTIVITAMIN PREPARATIONS

Cautions see individual vitamins; vitamin A concentration of preparations varies

Contra-indications see individual vitamins

Side-effects see individual vitamins

Licensed use Dalivit[®] not licensed for use in children under 6 weeks

Indications and dose

See under preparations below

Vitamins

Capsules, ascorbic acid 15 mg, nicotinamide 7.5 mg, riboflavin 500 micrograms, thiamine hydrochloride 1 mg, vitamin A 2500 units, vitamin D 300 units, net price 28-cap pack = £1.50

Dose

Prevention of deficiency

• By mouth

Child 1–12 years 1 capsule daily

Child 12–18 years 2 capsules daily

Cystic fibrosis: prevention of deficiency

• By mouth

Child 1–18 years 2–3 capsules daily

Abider[®] (Chefaro UK)

Drops, vitamins A, B group, C, and D. Net price 25 mL (with dropper) = £3.33

Note Contains 1333 units of vitamin A (as palmitate) per 0.6 mL dose

Excipients include arachis (peanut) oil and sucrose

Vitamin and mineral supplements and adjuncts to synthetic diets

Forceval[®] (Alliance)

Capsules, brown/red, vitamins (ascorbic acid 60 mg, biotin 100 micrograms, cyanocobalamin 3 micrograms, folic acid 400 micrograms, nicotinamide 18 mg, pantothenic acid 4 mg, pyridoxine 2 mg, riboflavin 1.6 mg, thiamine 1.2 mg, vitamin A 2500 units, vitamin D₂ 400 units, vitamin E 10 mg, minerals and trace elements (calcium 100 mg, chromium 200 micrograms, copper 2 mg, iodine 140 micrograms, iron 12 mg, magnesium 30 mg, manganese 3 mg, molybdenum 250 micrograms, phosphorus 77 mg, potassium 4 mg, selenium 50 micrograms, zinc 15 mg), net price 15-cap pack = £3.40, 30-cap pack = £5.93, 90-cap pack = £14.32. Label: 25

Dose

Vitamin and mineral deficiency and as adjunct in synthetic diets

Child 12–18 years 1 capsule daily one hour after a meal

Ketovite[®] (Essential)

Tablets (PoM), yellow, ascorbic acid 16.6 mg, riboflavin 1 mg, thiamine hydrochloride 1 mg, pyridoxine hydrochloride 330 micrograms, nicotinamide 3.3 mg, calcium pantothenate 1.16 mg, alpha tocopheryl acetate 5 mg, inositol 50 mg, biotin 170 micrograms, folic acid 250 micrograms, acetomenaphthone 500 micrograms, net price 100-tab pack = £9.21

Dose

Prevention of vitamin deficiency in disorders of carbohydrate or amino-acid metabolism and adjunct in restricted, specialised, or synthetic diets

Child 1 month–18 years 1 tablet 3 times daily: dose adjusted according to condition, diet, or age; use with Ketovite[®] Liquid for complete vitamin supplementation

Administration may be crushed immediately before use

Liquid, pink, sugar-free, vitamin A 2500 units, ergocalciferol 400 units, choline chloride 150 mg, cyanobalamin 12.5 micrograms/5 mL, net price 150-mL pack = £19.10

Dose

Prevention of vitamin deficiency in disorders of carbohydrate or amino-acid metabolism and adjunct in restricted, specialised, or synthetic diets

Child 1 month–18 years 5 mL daily; dose adjusted according to condition, diet, or age; use with *Ketovite*®
Tablets for complete vitamin supplementation

Administration may be mixed with milk, cereal, or fruit juice

9.7 Bitters and tonics

Classification not included in *BNF for Children*.

9.8 Metabolic disorders

9.8.1 Drugs used in metabolic disorders

9.8.2 Acute porphyrias

This section covers drugs used in metabolic disorders and not readily classified elsewhere.

9.8.1 Drugs used in metabolic disorders

Metabolic disorders should be managed under the guidance of a specialist. As many preparations are unlicensed and may be difficult to obtain, arrangements for continued prescribing and supply should be made in primary care.

General advice on the use of medicines in metabolic disorders can be obtained from:

Alder Hey Children's Hospital
Medicines Information Centre
Tel: (0151) 252 5381

and

Great Ormond Street Hospital for Children
Pharmacy
Tel: (020) 7405 9200

Wilson's disease

Penicillamine is used in Wilson's disease (hepatolenticular degeneration) to aid the elimination of copper ions; it is also used for cystinuria. Children who are hypersensitive to penicillin may react rarely to penicillamine.

Trientine is used for the treatment of Wilson's disease only, in patients intolerant of penicillamine; it is **not** an alternative to penicillamine in other diseases such as cystinuria. Penicillamine-induced systemic lupus erythematosus may not resolve on transfer to trientine.

Zinc prevents the absorption of copper in Wilson's disease. Symptomatic patients should be treated initially with a chelating agent because zinc has a slow onset of action. When transferring from chelating treatment to zinc maintenance therapy, chelating treatment should be co-administered for 2–3 weeks until zinc produces its maximal effect.

PENICILLAMINE

Cautions concomitant nephrotoxic drugs (increased risk of toxicity); monitor urine for proteinuria; monitor blood and platelet count regularly (see below); neurological involvement in Wilson's disease; **interactions:** Appendix 1 (penicillamine)

Blood counts and urine tests Consider withdrawal if platelet count falls below 120 000/mm³ or white blood cells below 2500/mm³ or if 3 successive falls within reference range (can restart at reduced dose when counts return to within reference range but permanent withdrawal necessary if recurrence of leucopenia or thrombocytopenia)

Counselling Warn child and carer to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, or rashes develop

Contra-indications lupus erythematosus

Renal impairment reduce dose and monitor renal function or avoid—consult product literature

Pregnancy fetal abnormalities reported rarely; avoid if possible

Breast-feeding manufacturer advises avoid unless potential benefit outweighs risk—no information available

Side-effects initially nausea, anorexia, fever, rash; proteinuria, thrombocytopenia; *rarely* mouth ulceration, stomatitis, male and female breast enlargement, haematuria (withdraw immediately if cause unknown), alopecia, pseudoxanthoma elasticum, elastosis perforans, skin laxity; *also reported* pancreatitis, vomiting, cholestatic jaundice, pulmonary haemorrhage, bronchiolitis, pneumonitis, neuropathy (especially if neurological involvement in Wilson's disease—prophylactic pyridoxine recommended, see section 9.6.2), taste loss (mineral supplements not recommended), blood disorders including neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia and leucopenia, nephrotic syndrome, glomerulonephritis, Goodpasture's syndrome, lupus erythematosus, myasthenia gravis, polymyositis, rheumatoid arthritis, urticaria, dermatomyositis, pemphigus, Stevens-Johnson syndrome, late rashes (consider dose reduction)

Indications and dose

Wilson's disease

• By mouth

Child 1 month–18 years 20 mg/kg (max. 2 g) daily in 2–3 divided doses 1 hour before food; usual maintenance dose for child over 12 years 0.75–1 g daily

Cystinuria

• By mouth

Child 1 month–18 years 20–30 mg/kg (max. 3 g) daily in 2–3 divided doses 1 hour before food (lower doses may be used initially and increased gradually), adjusted to maintain 24-hour urinary cystine below 1 mmol/litre; maintain adequate fluid intake

Penicillamine (Non-proprietary) (PoM)

Tablets, penicillamine 125 mg, net price 56-tab pack = £11.20; 250 mg, 56-tab pack = £21.68. Label: 6, 22, counselling, blood disorder symptoms (see above)

Distamine® (Alliance) (PoM)

Tablets, all f/c, penicillamine 125 mg, net price 100 = £10.34; 250 mg, 100 = £17.78. Label: 6, 22, counselling, blood disorder symptoms (see above)

TRIENTINE DIHYDROCHLORIDE

Cautions see notes above; **interactions:** Appendix 1 (trientine)

Pregnancy teratogenic in *animal* studies—use only if benefit outweighs risk; monitor maternal and neonatal serum-copper concentrations

Side-effects nausea, rash; *very rarely* anaemia; duodenitis and colitis also reported

Indications and dose

Wilson's disease in patients intolerant of penicillamine

- By mouth

Child 2–12 years 0.6–1.5 g daily in 2–4 divided doses before food, adjusted according to response

Child 12–18 years 1.2–2.4 g daily in 2–4 divided doses before food, adjusted according to response

Trientine Dihydrochloride (Univar) (PoM)

Capsules, trientine dihydrochloride 300 mg. Label: 22

ZINC ACETATE

Cautions portal hypertension (risk of hepatic decompensation when switching from chelating agent); monitor full blood count and serum cholesterol; **interactions:** Appendix 1 (zinc)

Pregnancy usual dose 25 mg 3 times daily adjusted according to plasma-copper concentration and urinary copper excretion

Breast-feeding manufacturer advises avoid; present in milk—may cause zinc-induced copper deficiency in infant

Side-effects gastric irritation (usually transient; may be reduced if first dose taken mid-morning or with a little protein); *less commonly* sideroblastic anaemia and leucopenia

Indications and dose

Dose expressed as elemental zinc

Wilson's disease

- By mouth

Child 1–6 years 25 mg twice daily

Child 6–16 years body-weight under 57 kg, 25 mg 3 times daily; body-weight 57 kg or over, 50 mg 3 times daily

Child 16–18 years 50 mg 3 times daily

Wilzin® (Orphan Europe) (PoM)

Capsules, zinc (as acetate) 25 mg (blue), net price 250-cap pack = £132.00; 50 mg (orange), 250-cap pack = £242.00. Label: 23

Administration capsules may be opened and the contents mixed with water

Carnitine deficiency

Levocarnitine is available for the management of primary carnitine deficiency due to inborn errors of metabolism, or of secondary deficiency in haemodialysis patients.

Levocarnitine is also used in the treatment of some organic acidurias; however, use in fatty acid oxidation is controversial.

LEVOCARNITINE

(Carnitine)

Cautions diabetes mellitus; monitoring of free and acyl carnitine in blood and urine recommended

Renal impairment accumulation of metabolites may occur with chronic oral administration in severe impairment

Pregnancy appropriate to use; no evidence of teratogenicity in *animal* studies

Side-effects nausea, vomiting, abdominal pain, diarrhoea, fishy body odour; side-effects may be dose-related—monitor tolerance during first week and after any dose increase

Licensed use not licensed for use by intravenous infusion; tablets, chewable tablets, and oral liquid (10%) not licensed in children under 12 years; paediatric oral solution (30%) not licensed in children over 12 years; not licensed for use in organic acidurias

Indications and dose

Primary deficiency and organic acidurias

- By mouth

Neonate up to 200 mg/kg daily in 2–4 divided doses

Child 1 month–18 years up to 200 mg/kg daily in 2–4 divided doses; usual max. 3 g daily

- By intravenous infusion

Neonate initially 100 mg/kg over 30 minutes followed by a continuous infusion of 4 mg/kg/hour

Child 1 month–18 years initially 100 mg/kg over 30 minutes followed by a continuous infusion of 4 mg/kg/hour

- By slow intravenous injection over 2–3 minutes

Neonate up to 100 mg/kg/daily in 2–4 divided doses

Child 1 month–18 years up to 100 mg/kg/daily in 2–4 divided doses

Secondary deficiency in dialysis patients

- By slow intravenous injection over 2–3 minutes

Child 1 month–18 years 20 mg/kg after each dialysis session, adjusted according to plasma-carnitine concentration

- By mouth

(maintenance therapy if benefit gained from first intravenous course)

Child 1 month–18 years 1 g daily

Administration for *intravenous infusion*, dilute injection with Sodium Chloride 0.9% or Glucose 5% or 10%

Levocarnitine (Non-proprietary) (PoM)

Paediatric oral solution, levocarnitine 300 mg/mL (30%), net price 20 mL = £55.55

Carnitor® (Sigma-Tau) (PoM)

Tablets, levocarnitine 330 mg, net price 90-tab pack = £103.95

Chewable tablets, levocarnitine 1 g, net price 10-tab pack = £35.00

Oral liquid, levocarnitine 100 mg/mL (10%), net price 10 × 10-mL (1-g) single-dose bottle = £35.00

Injection, levocarnitine 200 mg/mL, net price 5-mL amp = £11.90

Fabry's disease

Agalsidase alfa and **agalsidase beta**, enzymes produced by recombinant DNA technology, are licensed for long-term enzyme replacement therapy in Fabry's disease (a lysosomal storage disorder caused by deficiency of alpha-galactosidase A).

AGALSIDASE ALFA and BETA

Cautions interactions: Appendix 1 (agalsidase alfa and beta)

Infusion-related reactions Infusion-related reactions very common; manage by slowing the infusion rate or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature

Pregnancy use with caution

Breast-feeding use with caution—no information available

Side-effects gastro-intestinal disturbances, taste disturbances; tachycardia, bradycardia, palpitation, hypertension, hypotension, chest pain, oedema, flushing; dyspnoea, cough, rhinorrhoea; headache, fatigue, dizziness, asthma, paraesthesia, syncope, neuropathic pain, tremor, sleep disturbances; influenza-like symptoms, nasopharyngitis; muscle spasms, myalgia, arthralgia; eye irritation; tinnitus; hypersensitivity reactions, angioedema, pruritus, urticaria, rash, acne; *less commonly* cold extremities, parosmia, ear pain and swelling, skin discoloration, and injection-site reactions

Indications and dose

Fabry's disease (specialist use only)

see under preparations

Fabrazyme® (Genzyme) PoM

Intravenous infusion, powder for reconstitution, agalsidase beta, net price 5-mg vial = £315.08; 35-mg vial = £2196.59

Dose

Fabry's disease (specialist use only)

• By intravenous infusion

Child 8–18 years 1 mg/kg every 2 weeks

Administration for *intravenous infusion*, reconstitute initially with Water for Injections (5 mg in 1.1 mL, 35 mg in 7.2 mL) to produce a solution containing 5 mg/mL; dilute with Sodium Chloride 0.9% (for doses less than 35 mg dilute with at least 50 mL; doses 35–70 mg dilute with at least 100 mL; doses 70–100 mg dilute with at least 250 mL; doses greater than 100 mg dilute with 500 mL) and give through an in-line low protein-binding 0.2 micron filter at an initial rate of no more than 15 mg/hour; for subsequent infusions, infusion rate may be increased gradually once tolerance has been established

Replagal® (Shire HGT) PoM

Concentrate for intravenous infusion, agalsidase alfa 1 mg/mL, net price 1-mL vial = £356.85; 3.5-mL vial = £1068.64

Dose

Fabry's disease (specialist use only)

• By intravenous infusion

Child 7–18 years 200 micrograms/kg every 2 weeks

Administration for *intravenous infusion*, dilute requisite dose with 100 mL Sodium Chloride 0.9% and give over 40 minutes using an in-line filter; use within 3 hours of dilution

Gaucher's disease

Imiglucerase, an enzyme produced by recombinant DNA technology, is administered as enzyme replacement therapy in Gaucher's disease, a familial disorder affecting principally the liver, spleen, bone marrow, and lymph nodes.

Velaglucerase alfa, an enzyme produced by recombinant DNA technology, is administered as enzyme replacement therapy for the treatment of type I Gaucher's disease.

Miglustat, an inhibitor of glucosylceramide synthase, is licensed in adults for the treatment of mild to moderate type I Gaucher's disease in patients for whom imiglucerase is unsuitable; it is given by mouth.

IMIGLUCERASE

Cautions monitor for imiglucerase antibodies; when stabilised, monitor all parameters and response to treatment at intervals of 6–12 months

Pregnancy manufacturer advises use with caution—limited information available

Breast-feeding no information available

Side-effects hypersensitivity reactions (including urticaria, angioedema, cyanosis, hypotension, flushing, tachycardia, paraesthesia, backache); *less commonly* nausea, vomiting, diarrhoea, abdominal cramps, fatigue, headache, dizziness, fever, arthralgia, injection-site reactions

Indications and dose

Gaucher's disease type I (specialist use only)

• By intravenous infusion

Neonate initially 60 units/kg once every 2 weeks, adjusted according to response; doses as low as 30 units/kg once every 2 weeks may be appropriate

Child 1 month–18 years initially 60 units/kg once every 2 weeks, adjusted according to response; doses as low as 30 units/kg once every 2 weeks may be appropriate

Gaucher's disease type III (specialist use only)

• By intravenous infusion

Neonate 60–120 units/kg once every 2 weeks, adjusted according to response

Child 1 month–18 years 60–120 units/kg once every 2 weeks, adjusted according to response

Administration For *intravenous infusion*, initially reconstitute with Water for Injections (200 units in 5.1 mL, 400 units in 10.2 mL) to a concentration of 40 units/mL; dilute requisite dose with Sodium Chloride 0.9% to a final volume of 100–200 mL; give initial dose at a rate not exceeding 0.5 units/kg/minute, subsequent doses to be given at a rate not exceeding 1 unit/kg/minute; administer within 3 hours of reconstitution

Cerezyme® (Genzyme) PoM

Intravenous infusion, powder for reconstitution, imiglucerase, net price 200-unit vial = £535.65; 400-unit vial = £1071.29

Electrolytes Na⁺ 0.62 mmol/200-unit vial, 1.24 mmol/400-unit vial

VELAGLUCERASE ALFA

Cautions monitor immunoglobulin G (IgG) antibody concentration in severe infusion-related reactions or if there is a lack or loss of effect with velaglucerase alfa
Infusion-related reactions Infusion-related reactions very common; manage by slowing the infusion rate, or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature

Pregnancy manufacturer advises use with caution—limited information available

Breast-feeding manufacturer advises use with caution—no information available

Side-effects nausea, abdominal pain, tachycardia, hypertension, hypotension, flushing, headache, dizziness, malaise, pyrexia, arthralgia, bone pain, back pain, hypersensitivity reactions, rash, urticaria

Indications and dose

Gaucher's disease type I (specialist use only)

- By intravenous infusion

Child 4–18 years 60 units/kg once every 2 weeks; adjusted according to response to 15–60 units/kg once every 2 weeks

Administration for *intravenous infusion*, reconstitute each 400-unit vial with 4.3 mL water for injections; dilute requisite dose in 100 mL Sodium Chloride 0.9% and give over 60 minutes through a 0.22 micron filter; start infusion within 24 hours of reconstitution

VPRIV® (Shire HGT) ▼ (PoM)

Intravenous infusion, powder for reconstitution, velaglucerase alfa, net price 400-unit vial = £1410.20

Electrolytes Na⁺ 0.53 mmol/400-unit vial

Mucopolysaccharidosis

Laronidase, an enzyme produced by recombinant DNA technology, is licensed for long-term replacement therapy in the treatment of non-neurological manifestations of mucopolysaccharidosis I, a lysosomal storage disorder caused by deficiency of alpha-L-iduronidase.

Idursulfase, an enzyme produced by recombinant DNA technology, is licensed for long-term replacement therapy in mucopolysaccharidosis II (Hunter syndrome), a lysosomal storage disorder caused by deficiency of iduronate-2-sulfatase.

Galsulfase, a recombinant form of human N-acetylglucosamine-4-sulfatase, is licensed for long-term replacement therapy in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome).

Infusion-related reactions Infusion-related reactions often occur with administration of laronidase, idursulfase, and galsulfase; they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature for details.

GALSULFASE

Cautions respiratory disease; acute febrile or respiratory illness (consider delaying treatment)

Infusion-related reactions See notes above

Pregnancy manufacturer advises avoid unless essential

Breast-feeding manufacturer advises avoid—no information available

Side-effects abdominal pain, umbilical hernia, gastroenteritis; chest pain, hypertension; dyspnoea, apnoea, nasal congestion; rigors, malaise, areflexia; pharyngitis; conjunctivitis, corneal opacity; ear pain; facial oedema

Indications and dose

Mucopolysaccharidosis VI (specialist use only)

- By intravenous infusion

Child 5–18 years 1 mg/kg once weekly

Administration for *intravenous infusion*, dilute requisite dose with Sodium Chloride 0.9% to a final volume of 250 mL and mix gently; infuse through a 0.2 micron in-line filter; give approx. 2.5% of the total volume over 1 hour, then infuse remaining volume over next 3 hours; if body-weight under 20 kg and at risk of fluid overload, dilute requisite dose in 100 mL Sodium Chloride 0.9% and give over at least 4 hours

Naglazyme® (BioMarin) (PoM)

Concentrate for intravenous infusion, galsulfase 1 mg/mL, net price 5-mL vial = £982.00

IDURSULFASE

Cautions severe respiratory disease; acute febrile respiratory illness (consider delaying treatment)

Infusion-related reactions See notes above

Contra-indications women of child-bearing potential

Pregnancy manufacturer advises avoid

Breast-feeding manufacturer advises avoid—present in milk in animal studies

Side-effects gastro-intestinal disturbances, swollen tongue; arrhythmia, tachycardia, chest pain, cyanosis, peripheral oedema, hypertension, hypotension, flushing; bronchospasm, hypoxia, cough, wheezing, tachypnoea, dyspnoea; headache, dizziness, tremor; pyrexia; arthralgia; facial oedema, urticaria, pruritus, rash, infusion-site swelling, erythema; pulmonary embolism and anaphylaxis also reported

Indications and dose

Mucopolysaccharidosis II (specialist use only)

- By intravenous infusion

Child 5–18 years 500 micrograms/kg once weekly

Administration for *intravenous infusion*, dilute requisite dose in 100 mL Sodium Chloride 0.9% and mix gently (do not shake); give over 3 hours (gradually reduced to 1 hour if no infusion-related reactions)

Elaprase® (Shire HGT) ▼ (PoM)

Concentrate for intravenous infusion, idursulfase 2 mg/mL, net price 3-mL vial = £1985.00

LARONIDASE

Cautions monitor immunoglobulin G (IgG) antibody concentration; **interactions:** Appendix 1 (laronidase)
Infusion-related reactions See notes above

Pregnancy manufacturer advises avoid unless essential—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, diarrhoea, abdominal pain; cold extremities, pallor, flushing, tachycardia, blood pressure changes; dyspnoea, cough, angioedema, anaphylaxis; headache, paraesthesia, dizziness, fatigue, restlessness; influenza-like symptoms; musculoskeletal pain, pain in extremities; rash, pruritus, urticaria, alopecia, infusion-site reactions; bronchospasm and respiratory arrest also reported

Indications and dose

Non-neurological manifestations of mucopolysaccharidosis I (specialist use only)

• By intravenous infusion

Child 1 month–18 years 100 units/kg once weekly

Administration for intravenous infusion, dilute with Sodium Chloride 0.9%; body-weight under 20 kg, dilute to 100 mL, body-weight over 20 kg dilute to 250 mL; give through in-line filter (0.22 micron) initially at a rate of 2 units/kg/hour then increase gradually every 15 minutes to max. 43 units/kg/hour

Alidurzyme (Genzyme) (PoM)

Concentrate for intravenous infusion, laronidase 100 units/mL, net price 5-mL vial = £444.70

Electrolytes Na⁺ 1.29 mmol/5-mL vial

Nephropathic cystinosis

Mercaptamine is available for the treatment of nephropathic cystinosis. The oral dose is increased over several weeks to avoid intolerance. Mercaptamine has a very unpleasant taste and smell, which can affect compliance.

All patients receiving mercaptamine should be registered (contact local specialist centre for details).

Mercaptamine eye drops are used in the management of ocular symptoms arising from the deposition of cystine crystals in the eye.

Safe Practice

Mercaptamine has been confused with mercaptopurine; care must be taken to ensure the correct drug is prescribed and dispensed.

MERCAPTAMINE (Cysteamine)

Cautions leucocyte-cystine concentration and haematological monitoring required—consult product literature; dose of phosphate supplement may need to be adjusted if transferring from phosphocysteamine to mercaptamine

Contra-indications hypersensitivity to penicillamine

Pregnancy avoid—teratogenic and toxic in animal studies

Breast-feeding avoid

Side-effects breath and body odour, nausea, vomiting, diarrhoea, anorexia, abdominal pain, gastroenteritis, dyspepsia, encephalopathy, headache, malaise, fever, rash; *less commonly* gastro-intestinal ulcer, seizures, hallucinations, drowsiness, nervousness, leucopenia, nephrotic syndrome

Licensed use eye drops not licensed

Indications and dose

Nephropathic cystinosis (specialist use only)

• By mouth

Neonate initially one-sixth to one-quarter of the expected maintenance dose, increased gradually over 4–6 weeks; maintenance, 1.3 g/m² (approx. 50 mg/kg) daily in 4 divided doses

Child 1 month–12 years or under 50 kg initially one-sixth to one-quarter of the expected maintenance dose, increased gradually over 4–6 weeks; maintenance, 1.3 g/m² (approx. 50 mg/kg) daily in 4 divided doses

Child 12–18 years or over 50 kg initially one-sixth to one-quarter of the expected maintenance dose, increased gradually over 4–6 weeks; maintenance, 2 g daily in 4 divided doses

Cystagon[®] (Orphan Europe) (PoM)

Capsules, mercaptamine (as bitartrate) 50 mg, net price 100-cap pack = £70.00; 150 mg, 100-cap pack = £190.00. Label: 21

Note For child under 6 years at risk of aspiration, capsules can be opened and contents sprinkled on food (at a temperature suitable for eating); avoid adding to acidic drinks (e.g. orange juice)

■ Eye drops

Mercaptamine (Non-proprietary)

Eye drops, mercaptamine 0.11% and 0.55%, 10 mL. Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Pompe disease

Alglucosidase alfa, an enzyme produced by recombinant DNA technology, is licensed for long-term replacement therapy in Pompe disease, a lysosomal storage disorder caused by deficiency of acid alpha-glucosidase.

ALGLUCOSIDASE ALFA

Cautions cardiac and respiratory dysfunction—monitor closely; monitor immunoglobulin G (IgG) antibody concentration

Infection-related reactions Infusion-related reactions very common, calling for use of antihistamine, antipyretic, or corticosteroid; consult product literature for details

Pregnancy toxicity in animal studies, but treatment should not be withheld

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, diarrhoea; flushing, tachycardia, blood pressure changes, cold extremities, cyanosis, facial oedema, chest discomfort; cough, tachypnoea, bronchospasm; headache, agitation, tremor, irritability, restlessness, paraesthesia, dizziness, fatigue; pyrexia; antibody formation; myalgia, muscle spasms; sweating, rash, pruritus, urticaria, injection-site reactions; hypersensitivity reactions (including anaphylaxis); severe skin reactions (including ulcerative and necrotising skin lesions) also reported

Indications and dose

Pompe disease (specialist use only)

• By intravenous infusion

Neonate 20 mg/kg every 2 weeks

Child 1 month–18 years 20 mg/kg every 2 weeks

Administration For intravenous infusion, reconstitute 50 mg with 10.3 mL Water for Injections to produce 5 mg/mL solution; gently rotate vial without shaking; dilute requisite dose with Sodium Chloride 0.9% to

give a final concentration of 0.5–4 mg/mL; give through a low protein-binding in-line filter (0.2 micron) at an initial rate of 1 mg/kg/hour increased by 2 mg/kg/hour every 30 minutes to max. 7 mg/kg/hour

Myozyme® (Genzyme) PoM

Intravenous infusion, powder for reconstitution, alglucosidase alfa, net price 50-mg vial = £356.06

Urea cycle disorders

Sodium benzoate and **sodium phenylbutyrate** are used in the management of urea cycle disorders. Both, either singly or in combination, are indicated as adjunctive therapy in all patients with neonatal-onset disease and in those with late-onset disease who have a history of hyperammonaemic encephalopathy. Sodium benzoate is also used in non-ketotic hyperglycinaemia.

Gastro-intestinal side-effects of urea benzoate or sodium phenylbutyrate may be reduced by giving smaller doses more frequently. The preparations contain significant amounts of sodium; therefore, they should be used with caution in children with congestive heart failure, renal insufficiency and clinical conditions involving sodium retention with oedema.

The long-term management of urea cycle disorders includes oral maintenance treatment with sodium benzoate and sodium phenylbutyrate combined with a low protein diet and other drugs such as **arginine** or **citrulline**, depending on the specific disorder.

Carglumic acid is licensed for the treatment of hyperammonaemia due to *N*-acetylglutamate synthase deficiency and organic acidaemia.

Emergency management

For further information on the emergency management of urea cycle disorders consult the British Inherited Metabolic Disease Group (BIMDG) website at www.bimdg.org.uk.

ARGININE

Cautions monitor plasma pH and chloride

Contra-indications not to be used in the treatment of arginase deficiency

Pregnancy no information available

Breast-feeding no information available

Side-effects intravenous injection only: nausea, vomiting; flushing, hypotension; headache, numbness; hyperchloraemic metabolic acidosis; irritation at injection-site

Licensed use injection and tablets not licensed in children; powder licensed for urea cycle disorders in children

Indications and dose

Acute hyperammonaemia in carbamylphosphate synthetase deficiency, ornithine transcarbamylase deficiency (specialist use only). See also notes above

• By intravenous infusion

Neonate 6 mg/kg/hour

Child 1 month–18 years

Body-weight under 40 kg 6 mg/kg/hour

Body-weight over 40 kg 4 mg/kg/hour

Maintenance treatment of hyperammonaemia in carbamylphosphate synthetase deficiency, ornithine transcarbamylase deficiency (specialist use only)

• By mouth

Neonate 100–200 mg/kg daily in 3–4 divided doses with feeds

Child 1 month–18 years

Body-weight under 20 kg 100–200 mg/kg daily in 3–4 divided doses with feeds or meals

Body-weight over 20 kg 2.5–6 g/m² daily in 3–4 divided doses with meals (max. 6 g daily)

Acute hyperammonaemia in citrullinaemia, argininosuccinic aciduria (specialist use only). See also notes above

• By intravenous infusion

Neonate initially 300 mg/kg over 90 minutes followed by 12.5 mg/kg/hour over 24 hours (max. 25 mg/kg/hour thereafter)

Child 1 month–18 years

Body-weight under 40 kg initially 300 mg/kg over 90 minutes followed by 12.5 mg/kg/hour over 24 hours (max. 25 mg/kg/hour thereafter)

Body-weight over 40 kg 21 mg/kg/hour

Maintenance treatment of hyperammonaemia in citrullinaemia, argininosuccinic aciduria (specialist use only)

• By mouth

Neonate 100–300 mg/kg daily in 3–4 divided doses with feeds

Child 1 month–18 years

Body-weight under 20 kg 100–300 mg/kg daily in 3–4 divided doses with feeds or meals

Body-weight over 20 kg 2.5–6 g/m² daily in 3–4 divided doses with meals (max. 6 g daily)

L-Arginine (Non-proprietary)

Tablets, L-arginine (as hydrochloride) 500 mg.

Oral solution, L-arginine 100 mg/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Powder, L-arginine (as hydrochloride), net price 100 g = £12.23

Prescribe as a borderline substance (ACBS). For use as a supplement in urea cycle disorders other than arginase deficiency, such as hyperammonaemia types I and II, citrullinaemia, argininosuccinic aciduria, and deficiency of *N*-acetyl glutamate synthetase

Injection, L-arginine (as hydrochloride) 500 mg/mL, 10-mL ampoules; 100 mg/mL, 200-mL amp

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Note Other strengths may be available from 'special-order' manufacturers or specialist importing companies, see p. 840

Administration dilute to a max. concentration of 50 mg/mL with glucose 10%

CARGLUMIC ACID

Pregnancy manufacturer advises avoid unless essential—no information available

Breast-feeding manufacturer advises avoid—present in milk in animal studies

Side-effects sweating; less commonly diarrhoea, vomiting, bradycardia, pyrexia

Indications and dose

Hyperammonaemia due to *N*-acetyl glutamate synthase deficiency (under specialist supervision). See also notes above

- By mouth

Neonate initially 50–125 mg/kg twice daily immediately before feeds, adjusted according to plasma-ammonia concentration; maintenance 5–50 mg/kg twice daily; total daily dose may alternatively be given in 3–4 divided doses

Child 1 month–18 years initially 50–125 mg/kg twice daily immediately before food, adjusted according to plasma-ammonia concentration; maintenance 5–50 mg/kg twice daily; total daily dose may alternatively be given in 3–4 divided doses

Hyperammonaemia due to organic acidaemia (under specialist supervision)

- By mouth

Neonate initially 50–125 mg/kg twice daily immediately before feeds, adjusted according to plasma-ammonia concentration; total daily dose may alternatively be given in 3–4 divided doses

Child 1 month–18 years initially 50–125 mg/kg twice daily immediately before food, adjusted according to plasma-ammonia concentration; total daily dose may alternatively be given in 3–4 divided doses

Carbaglu® (Orphan Europe) (PoM)

Dispersible tablets, carginic acid 200 mg, net price 5-tab pack = £299.00, 60-tab pack = £3499.00.

Label: 13

Administration Must be dispersed in at least 5–10 mL of water and taken orally immediately, or administered via a nasogastric tube

CITRULLINE

Pregnancy no information available

Breast-feeding no information available

Indications and dose

Carbamyl phosphate synthase deficiency, ornithine carbamyl transferase deficiency

- By mouth

Neonate 150 mg/kg daily in 3–4 divided doses, adjusted according to response

Child 1 month–18 years 150 mg/kg daily in 3–4 divided doses, adjusted according to response

Citrulline Powder (Non-proprietary)

Powder, L-citrulline 100 g

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Administration May be mixed with drinks or taken as a paste

SODIUM BENZOATE

Cautions see notes above; neonates (risk of kernicterus and increased side-effects); **interactions:** Appendix 1 (sodium benzoate)

Renal impairment see notes above

Pregnancy no information available

Breast-feeding no information available

Side-effects nausea, vomiting, anorexia; irritability, lethargy, coma

Licensed use not licensed for use in children

Indications and dose

Acute hyperammonaemia due to urea cycle disorders (specialist use only). See also notes above

- By intravenous infusion

Neonate initially 250 mg/kg over 90 minutes followed by 10 mg/kg/hour, adjusted according to response

Child 1 month–18 years initially 250 mg/kg over 90 minutes followed by 10 mg/kg/hour, adjusted according to response

Maintenance treatment of hyperammonaemia due to urea cycle disorders; non-ketotic hyperglycinaemia (specialist use only)

- By mouth

Neonate up to 250 mg/kg daily in 3–4 divided doses with feeds

Child 1 month–18 years up to 250 mg/kg daily in 3–4 divided doses with feeds or meals (max. 12 g daily)

Administration for administration *by mouth*, oral solution or powder may be administered in fruit drinks; less soluble in acidic drinks

Sodium Benzoate (Non-proprietary) (PoM)

Tablets, sodium benzoate 500 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Capsules, sodium benzoate 50 mg; 250 mg; 400 mg; 500 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Oral solution, sodium benzoate 100 mg/mL; 200 mg/mL; 300 mg/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Injection, sodium benzoate 200 mg/mL, 5-mL amp

Note Contains Na⁺ 1.4 mmol/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Administration for *intravenous infusion*, dilute to a max. concentration of 50 mg/mL with Glucose 10%

SODIUM PHENYLBUTYRATE

Cautions see notes above; congestive heart failure; **interactions:** Appendix 1 (sodium phenylbutyrate)

Hepatic impairment manufacturer advises use with caution

Renal impairment manufacturer advises use with caution; see also notes above

Pregnancy avoid—toxicity in *animal* studies; manufacturer advises adequate contraception in women of child-bearing potential

Breast-feeding manufacturer advises avoid—no information available

Side-effects amenorrhoea and irregular menstrual cycles, decreased appetite, body odour, taste disturbances; less commonly nausea, vomiting, abdominal pain, peptic ulcer, pancreatitis, rectal bleeding, arrhythmia, oedema, syncope, depression, headache, rash, weight gain, renal tubular acidosis, aplastic anaemia, ecchymoses

Licensed use injection not licensed for use in children

Indications and dose

Acute hyperammonaemia due to urea cycle disorders (specialist use only). See also notes above

• By intravenous infusion

Neonate initially 250 mg/kg over 90 minutes followed by 10 mg/kg/hour adjusted according to response

Child 1 month–18 years initially 250 mg/kg over 90 minutes followed by 10 mg/kg/hour adjusted according to response

Maintenance treatment of hyperammonaemia due to urea cycle disorders (specialist use only)

• By mouth

Neonate up to 250 mg/kg daily in 3–4 divided doses with feeds

Child 1 month–18 years

Body-weight under 20 kg up to 250 mg/kg daily in 3–4 divided doses with feeds or meals

Body-weight over 20 kg 5 g/m² daily in 3–4 divided doses with meals (max. 12 g daily)

Administration Oral dose may be mixed with fruit drinks, milk, or feeds

Sodium Phenylbutyrate (Non-proprietary) (PoM)

Injection, sodium phenylbutyrate 200 mg/mL, 5-mL amp

Note Contains Na⁺ 1.1 mmol/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Administration for intravenous infusion, dilute to a max. concentration of 50 mg/mL with Glucose 10%

Ammonaps® (Swedish Orphan) (PoM)

Tablets, sodium phenylbutyrate 500 mg. Contains Na⁺ 2.7 mmol/tablet. Net price 250-tab pack = £493.00

Granules, sodium phenylbutyrate 940 mg/g. Contains Na⁺ 5.4 mmol/g of sodium phenylbutyrate. Net price 266-g pack = £860.00

Note Granules should be mixed with food before taking

Pheburane® (Lucane) (PoM)

Granules, sodium phenylbutyrate 483 mg/g. Contains Na⁺ 5.4 mmol/g of sodium phenylbutyrate, net price 174-g pack = £331.00

Note Granules should be mixed with food before taking orally and must not be administered by nasogastric or gastrostomy tubes

Other metabolic disorders

Other metabolic disorders and the drugs used in their management include:

Amino acid disorders: maple syrup urine disease (thiamine section 9.6.2); tyrosinaemia type III, hawkinsinuria (Vitamin C, section 9.6.3); tyrosinaemia type I (nitisone).

Mitochondrial disorders: isolated carboxylase defects, defects of biotin metabolism (biotin, see below); mitochondrial myopathies (ubidecarenone); congenital lactic acidosis (riboflavin and thiamine, section 9.6.2); respiratory chain defects (thiamine, section 9.6.2); pyruvate dehydrogenase defects (sodium dichloroacetate)

Neimann-Pick type C disease: miglustat is available for the treatment of progressive neurological manifestations of Neimann-Pick type C disease, a neurodegen-

erative disorder characterised by impaired intracellular lipid trafficking.

Homocystinuria and defects in cobalamin metabolism: betaine, pyridoxine (section 9.6.2), hydroxocobalamin (section 9.1.2)

Tetrahydrofolate reductase deficiency: betaine, folic acid (section 9.1.2)

The *Scottish Medicines Consortium* (p. 3) has advised (July 2010) that betaine anhydrous (Cystadane®) is accepted for restricted use within NHS Scotland for the adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or cobalamin cofactor metabolism in patients who are not responsive to pyridoxine treatment.

BETAINE

Cautions monitor plasma-methionine concentration before and during treatment—interrupt treatment if symptoms of cerebral oedema occur

Pregnancy manufacturer advises avoid unless essential—limited information available

Breast-feeding manufacturer advises caution—no information available

Side-effects less commonly gastro-intestinal disorders, anorexia, reversible cerebral oedema (see Cautions), agitation, depression, personality disorder, sleep disturbances, urinary incontinence, alopecia, and urticaria

Indications and dose

Adjunctive treatment of homocystinuria (specialist use only)

• By mouth

Neonate 50 mg/kg twice daily, dose and frequency adjusted according to response; max. 75 mg/kg twice daily

Child 1 month–10 years 50 mg/kg twice daily, dose and frequency adjusted according to response; max. 75 mg/kg twice daily

Child 10–18 years 3 g twice daily, adjusted according to response; max. 10 g twice daily

Administration Powder should be mixed with water, juice, milk, formula, or food until completely dissolved and taken immediately; measuring spoons are provided to measure 1 g, 150 mg, and 100 mg of Cystadane® powder

Betaine (Non-proprietary) (PoM)

Powder (for oral solution), betaine anhydrous 500 mg/mL when reconstituted.

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Tablets, betaine anhydrous 500 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Cystadane® (Orphan Europe) (PoM)

Powder, betaine (anhydrous), net price 180 g = £347.00

BIOTIN

(Vitamin H)

Pregnancy no information available

Breast-feeding no information available

Indications and dose**Isolated carboxylase defects**

- By mouth or by slow intravenous injection

Neonate 5 mg once daily, adjusted according to response; usual maintenance 10–50 mg daily, higher doses may be required

Child 1 month–18 years 10 mg once daily, adjusted according to response; usual maintenance 10–50 mg daily but up to 100 mg daily may be required

Defects of biotin metabolism

- By mouth or by slow intravenous injection

Neonate 10 mg once daily adjusted according to response; usual maintenance 5–20 mg daily but higher doses may be required

Child 1 month–18 years 10 mg once daily adjusted according to response; usual maintenance 5–20 mg daily but higher doses may be required

Biotin (Non-proprietary) (PoM)

Tablets, biotin 5 mg, 20-tab pack

Injection, biotin 5 mg/mL

Available from 'special order' manufacturers or specialist importing companies, see p. 840

Administration For administration *by mouth*, tablets may be crushed and mixed with food or drink

MIGLUSTAT

Cautions monitor cognitive and neurological function, growth, and platelet count

Hepatic impairment manufacturer advises caution—no information available

Renal impairment child 12–18 years, initially 200 mg twice daily if estimated glomerular filtration rate 50–70 mL/minute/1.73 m²; child 12–18 years, initially 100 mg twice daily if estimated glomerular filtration rate 30–50 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; child under 12 years—consult product literature

Pregnancy manufacturer advises avoid (toxicity in *animal* studies)—effective contraception must be used during treatment; also men should avoid fathering a child during and for 3 months after treatment

Breast-feeding manufacturer advises avoid—no information available

Side-effects diarrhoea, flatulence, abdominal pain, dyspepsia, constipation, nausea, vomiting, anorexia, weight changes, tremor, dizziness, headache, peripheral neuropathy, ataxia, amnesia, hypoaesthesia, paraesthesia, insomnia, depression, chills, malaise, decreased libido, thrombocytopenia, muscle spasm and weakness

Indications and dose

Neimann-Pick type C disease (specialist supervision only)

- By mouth

Child 4–12 years

Body surface area less than 0.47 m² 100 mg once daily

Body surface area 0.47–0.73 m² 100 mg twice daily

Body surface area 0.73–0.88 m² 100 mg three times daily

Body surface area 0.88–1.25 m² 200 mg twice daily

Body surface area greater than 1.25 m² 200 mg three times daily

Child 12–18 years 200 mg three times daily

Zavesca® (Actelion) (PoM)

Capsules, miglustat 100 mg, net price 84-cap pack = £3934.17 (hospital only)

NITISINONE
(NTBC)

Cautions slit-lamp examination of eyes recommended before treatment; monitor liver function regularly; monitor platelet and white blood cell count every 6 months

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk—toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—adverse effect in *animal* studies

Side-effects thrombocytopenia, leucopenia, granulocytopenia; conjunctivitis, photophobia, corneal opacity, keratitis, eye pain; *less commonly* leucocytosis, blepharitis, pruritus, exfoliative dermatitis, and erythematous rash

Indications and dose

Hereditary tyrosinaemia type I (in combination with dietary restriction of tyrosine and phenylalanine)

- By mouth

Neonate initially 500 micrograms/kg twice daily, adjusted according to response; max. 2 mg/kg daily

Child 1 month–18 years initially 500 micrograms/kg twice daily, adjusted according to response; max. 2 mg/kg daily

Administration capsules can be opened and the contents suspended in a small amount of water or formula diet and taken immediately

Orfadin® (Swedish Orphan) (PoM)

Capsules, nitisinone 2 mg, net price 60-cap pack = £564.00; 5 mg, 60-cap pack = £1127.00; 10 mg, 60-cap pack = £2062.00

SODIUM DICHLOROACETATE

Pregnancy no information available

Breast-feeding no information available

Side-effects polyneuropathy on prolonged use; abnormal oxalate metabolism; metabolic acidosis

Indications and dose**Pyruvate dehydrogenase defects**

- By mouth

Neonate initially 12.5 mg/kg 4 times daily, adjusted according to response; up to 200 mg/kg daily may be required

Child 1 month–18 years initially 12.5 mg/kg 4 times daily, adjusted according to response; up to 200 mg/kg daily may be required

Sodium dichloroacetate (Non-proprietary) (PoM)

Powder (for oral solution), sodium dichloroacetate 50 mg/mL when reconstituted with water
Available from 'special-order' manufacturers or specialist importing companies, see p. 840

UBIDECARENONE

(Ubiquinone, Co-enzyme Q10)

Cautions may reduce insulin requirement in diabetes mellitus; **interactions:** Appendix 1 (ubidecarenone)

Hepatic impairment reduce dose in moderate and severe impairment

Side-effects nausea, diarrhoea, heartburn; rarely headache, irritability, agitation, dizziness

Licensed use not limited

Indications and dose**Mitochondrial disorders**

• By mouth

Neonate initially 5 mg once or twice daily with food, adjusted according to response, up to 200 mg daily may be required

Child 1 month–18 years initially 5 mg once or twice daily with food, adjusted according to response, up to 300 mg daily may be required

Ubidecarenone (Non-proprietary) (PoM)

Oral solution, ubidecarenone 50 mg/10 mL

Tablets, ubidecarenone 10 mg

Capsules, ubidecarenone 10 mg, 30 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

9.8.2 Acute porphyrias

The acute porphyrias (acute intermittent porphyria, variegated porphyria, hereditary coproporphyria, and 5-aminolaevulinic acid dehydratase deficiency porphyria) are hereditary disorders of haem biosynthesis; they have a prevalence of about 1 in 10 000 of the population.

Great care must be taken when prescribing for patients with acute porphyria, since certain drugs can induce acute porphyric crises. Since acute porphyrias are hereditary, relatives of affected individuals should be screened and advised about the potential danger of certain drugs. Acute attacks of porphyria are exceptionally rare before puberty. When acute porphyria is suspected in a child, support from an expert porphyria service should be sought.

Treatment of serious or life-threatening conditions should not be withheld from patients with acute porphyria. When there is no safe alternative, treatment should be started and urinary porphobilinogen excretion should be measured regularly; if it increases or symptoms occur, the drug can be withdrawn and the acute attack treated. If an acute attack of porphyria occurs during pregnancy, contact an expert porphyria service for further advice.

Haem arginate is administered by short intravenous infusion as haem replacement in moderate, severe, or unremitting acute porphyria crises.

The National Acute Porphyria Service (NAPS) provides clinical support and treatment with haem arginate from three centres (University Hospital of Wales, Addenbrooke's Hospital, and King's College Hospital). To access

the service telephone (029) 2074 7747 and ask for the Acute Porphyria Service.

HAEM ARGINATE

(Human hemin)

Pregnancy manufacturer advises avoid unless essential

Breast-feeding manufacturer advises avoid unless essential—no information available

Side-effects pain and thrombophlebitis at injection site; rarely hypersensitivity reactions and fever; also reported headache

Indications and dose

Acute porphyrias (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria)

• By intravenous infusion

Child 1 month–18 years 3 mg/kg once daily (max. 250 mg daily) for 4 days; if response inadequate, repeat 4-day course with close biochemical monitoring

Normosang® (Orphan Europe) ▼ (PoM)

Concentrate for intravenous infusion, haem arginate 25 mg/mL, net price 10-mL amp = £434.25

Administration administer over at least 30 minutes through a filter via large antebachial or central vein; dilute requisite dose in 100 mL Sodium Chloride 0.9% in glass bottle; administer within 1 hour after dilution; max. concentration 2.5 mg/mL

Drugs unsafe for use in acute porphyrias

The following list contains drugs on the UK market that have been classified as 'unsafe' in porphyria because they have been shown to be porphyrinogenic in animals or *in vitro*, or have been associated with acute attacks in patients. Absence of a drug from the following lists does not necessarily imply that the drug is safe. For many drugs no information about porphyria is available.

An up-to-date list of drugs considered **safe** in acute porphyrias is available at www.wmic.wales.nhs.uk/porphyria_info.php.

Further information may be obtained from www.porphyria-europe.org and also from:

Welsh Medicines Information Centre
University Hospital of Wales
Cardiff, CF14 4XW
Tel: (029) 2074 2979/3877

Note Quite modest changes in chemical structure can lead to changes in porphyrinogenicity but where possible general statements have been made about groups of drugs; these should be checked first.

Unsafe drug groups (check first)

Alkylating drugs ¹	Calcium channel blockers ⁵	Non-nucleoside reverse transcriptase inhibitors ¹	Taxanes ¹
Amfetamines	Contraceptives, hormonal ⁶	Progestogens ⁵	Thiazolidinediones ¹
Anabolic steroids	Ergot derivatives ⁷	Protease inhibitors ¹	Triazole antifungals ⁸
Antidepressants ²	Hormone replacement therapy ⁶	Sulfonamides ⁹	
Antihistamines ³	Imidazole antifungals ⁸	Sulfonylureas ¹⁰	
Barbiturates ⁴			

Unsafe drugs (check groups above first)

Aceclofenac	Dapsone	Methyldopa	Rifabutin ¹³
Alcohol	Dexfenfluramine	Metolazone	Rifampicin
Aminophylline	Disopyramide	Metirapone	Riluzole
Amiodarone	Disulfiram	Mifepristone	Risperidone
Aprepitant	Erythromycin	Minoxidil ¹⁴	Selegiline
Artemether with lumefantrine	Etamsylate	Mitotane	Spironolactone
Bexarotene	Ethosuximide	Nalidixic acid	Sulfinpyrazone
Bosentan	Etomidate	Nitrazepam	Tamoxifen
Bromocriptine	Fenfluramine	Nitrofurantoin	Telithromycin
Buspiron	Flupentixol	Orphenadrine	Temoporfin
Cabergoline	Flutamide	Oxcarbazepine	Tiagabine
Carbamazepine	Fosphenytoin	Oxybutynin	Tinidazole
Chloral hydrate ¹¹	Griseofulvin	Pentazocine ¹⁵	Topiramate
Chloramphenicol	Hydralazine	Pentoxifylline	Toremifene
Chloroform ¹²	Indapamide	Phenoxybenzamine	Trimethoprim
Clindamycin	Isometheptene mucate	Phenytoin	Valproate
Cocaine	Isoniazid ¹³	Pivmecillinam	Xipamide
Colistimethate sodium	Ketamine	Porfimer	Zidovudine ¹
Danazol	Mefenamic acid ¹⁴	Potassium canrenoate ¹⁶	Zuclopentixol
	Meprobamate	Raloxifene	

1. Contact Welsh Medicines Information Centre for further advice.
2. Includes tricyclic (and related) antidepressants and MAOIs; fluoxetine, duloxetine, venlafaxine, and trazodone thought to be safe.
3. Alimemazine, chlorphenamine, desloratadine, fexofenadine, ketotifen, loratadine, and promethazine thought to be safe.
4. Includes primidone and thiopental.
5. Amlodipine, felodipine, and nifedipine thought to be safe.
6. Progestogens are more porphyrinogenic than oestrogens; oestrogens may be safe at least in replacement doses. Progestogens should be avoided whenever possible by all young women susceptible to acute porphyria; however, when non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs risk. The risk of an acute attack is greatest in young women who have had a previous attack. Long-acting progestogen preparations should never be used in those at risk of acute porphyria.
7. Includes ergometrine (oxytocin probably safe) and pergolide.
8. Applies to oral and intravenous use; topical antifungals are thought to be safe due to low systemic exposure.
9. Includes co-trimoxazole and sulfasalazine.
10. Glipizide and glimepiride are thought to be safe.
11. Although evidence of hazard is uncertain, manufacturer advises avoid.
12. Small amounts in medicines probably safe.
13. Safety uncertain, contact Welsh Medicines Information Centre for further advice.
14. May be used with caution if safer alternative not available.
15. Buprenorphine, codeine, diamorphine, dihydrocodeine, fentanyl, methadone, morphine, oxycodone, pethidine, and tramadol are thought to be safe.
16. Evidence of hazard uncertain—contact Welsh Medicines Information Centre for further advice.

10 Musculoskeletal and joint diseases

10.1	Drugs used in rheumatic diseases	504
10.1.1	Non-steroidal anti-inflammatory drugs	504
10.1.2	Corticosteroids	510
10.1.2.1	Systemic corticosteroids	510
10.1.2.2	Local corticosteroid injections	511
10.1.3	Drugs that suppress the rheumatic disease process	512
10.1.4	Gout and cytotoxic-induced hyperuricaemia	518
10.1.5	Other drugs for rheumatic diseases	518
10.2	Drugs used in neuromuscular disorders	518
10.2.1	Drugs that enhance neuromuscular transmission	518
10.2.2	Skeletal muscle relaxants	520
10.3	Drugs for the treatment of soft-tissue disorders and topical pain relief	522
10.3.1	Enzymes	522
10.3.2	Rubefacients, topical NSAIDs, capsaicin, and poultices	522

This chapter also includes advice on the drug management of the following:

- dental and orofacial pain, p. 505
- extravasation, p. 522
- myasthenia gravis, p. 518
- soft-tissue and other musculoskeletal disorders, p. 504
- juvenile idiopathic arthritis and other inflammatory disorders, p. 504

For treatment of septic arthritis see Table 1, section 5.1.

10.1 Drugs used in rheumatic diseases

10.1.1	Non-steroidal anti-inflammatory drugs
10.1.2	Corticosteroids
10.1.3	Drugs that suppress the rheumatic disease process
10.1.4	Gout and cytotoxic-induced hyperuricaemia
10.1.5	Other drugs for rheumatic diseases

Juvenile idiopathic arthritis and other inflammatory disorders

Rheumatic diseases require symptomatic treatment to relieve pain, swelling, and stiffness, together with treatment to control and suppress disease activity. Treatment of juvenile idiopathic arthritis may involve non-steroidal anti-inflammatory drugs (NSAIDs) (section 10.1.1), a disease modifying antirheumatic drug (DMARD) (section 10.1.3) such as methotrexate or a cytokine modulator, and intra-articular, intravenous, or oral corticosteroids (section 10.1.2).

Soft-tissue and musculoskeletal disorders

The management of children with soft-tissue injuries and strains, and musculoskeletal disorders, may include temporary rest together with the local application of heat or cold, local massage and physiotherapy. For pain relief, **paracetamol** (section 4.7.1) is often adequate and should be used first. Alternatively, the lowest effective dose of a **NSAID** (e.g. ibuprofen) can be used. If pain relief with either drug is inadequate, both paracetamol (in a full dose appropriate for the child) and a low dose of a NSAID may be required.

10.1.1 Non-steroidal anti-inflammatory drugs

In *single doses* non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic activity comparable to that of paracetamol (section 4.7.1), but paracetamol is preferred.

In regular *full dosage* NSAIDs have both a lasting analgesic and an anti-inflammatory effect which makes them particularly useful for the treatment of continuous or regular pain associated with inflammation.

Choice Differences in anti-inflammatory activity between NSAIDs are small, but there is considerable variation in individual response and tolerance of these drugs. A large proportion of children will respond to any NSAID; of the others, those who do not respond to one may well respond to another. Pain relief starts soon after

taking the first dose and a full analgesic effect should normally be obtained within a week, whereas an anti-inflammatory effect may not be achieved (or may not be clinically assessable) for up to 3 weeks. However, in juvenile idiopathic arthritis NSAIDs may take 4–12 weeks to be effective. If appropriate responses are not obtained within these times, another NSAID should be tried. The availability of appropriate formulations needs to be considered when prescribing NSAIDs for children.

NSAIDs reduce the production of prostaglandins by inhibiting the enzyme cyclo-oxygenase. They vary in their selectivity for inhibiting different types of cyclo-oxygenase; selective inhibition of cyclo-oxygenase-2 is associated with less gastro-intestinal intolerance. However, in children gastro-intestinal symptoms are rare in those taking NSAIDs for short periods. The role of selective inhibitors of cyclo-oxygenase-2 is undetermined in children.

Ibuprofen and **naproxen** are propionic acid derivatives used in children:

Ibuprofen combines anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other NSAIDs but its anti-inflammatory properties are weaker.

Naproxen combines good efficacy with a low incidence of side-effects.

Diclofenac, **indometacin**, **mefenamic acid**, and **piroxicam** have properties similar to those of propionic acid derivatives:

Diclofenac is similar in efficacy to naproxen.

Indometacin has an action equal to or superior to that of naproxen, but with a high incidence of side-effects including headache, dizziness, and gastro-intestinal disturbances. It is rarely used in children and should be reserved for when other NSAIDs have been unsuccessful.

Mefenamic acid has minor anti-inflammatory properties. It has occasionally been associated with diarrhoea and haemolytic anaemia which require discontinuation of treatment.

Piroxicam is as effective as naproxen and has a long duration of action which permits once-daily administration. However, it has more gastro-intestinal side-effects than most other NSAIDs, and is associated with more frequent serious skin reactions (**important**: see CHMP advice, p. 510).

Meloxicam is a selective inhibitor of cyclo-oxygenase-2. Its use may be considered in adolescents intolerant to other NSAIDs.

Ketorolac can be used for the short-term management of postoperative pain (section 15.1.4.2).

Etoricoxib, a selective inhibitor of cyclo-oxygenase-2, is licensed for the relief of pain in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute gout in children aged 16 years and over.

For the role of **aspirin** in children, see section 2.9.

Dental and orofacial pain Most mild to moderate dental pain and inflammation is effectively relieved by **ibuprofen** or **diclofenac**. For information on the risks of serious gastro-intestinal side-effects see below.

For further information on the management of dental and orofacial pain, see p. 199.

Cautions and contra-indications NSAIDs should be used with caution in children with a history of hypersensitivity to any NSAID—which includes those in

whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by any NSAID. NSAIDs should also be used with caution in coagulation defects. Caution may also be required in children with allergic disorders, and also in children with connective-tissue disorders, see Side-effects below.

In children with cardiac impairment, caution is required since NSAIDs may impair renal function (see also Side-effects below). All NSAIDs are contra-indicated in severe heart failure. **Diclofenac** and the selective inhibitor of cyclo-oxygenase-2, **etoricoxib**, are contra-indicated in ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, and mild to severe heart failure. They should be used with caution in children with a history of cardiac failure, left ventricular dysfunction, hypertension, in children with oedema for any other reason, and in children with other risk factors for cardiovascular events. Other non-selective NSAIDs should be used with caution in uncontrolled hypertension, heart failure, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, and when used long term in children with risk factors for cardiovascular events.

NSAIDs and cardiovascular events

The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults, all NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those patients receiving high doses long term. A small increased thrombotic risk cannot be excluded in children.

In adults, **cyclo-oxygenase-2 selective inhibitors**, **diclofenac** (150 mg daily) and **ibuprofen** (2.4 g daily) are associated with an increased risk of thrombotic events. The increased risk for diclofenac is similar to that of **etoricoxib**. **Naproxen** (in adults, 1 g daily) is associated with a lower thrombotic risk, and lower doses of ibuprofen (in adults, 1.2 g daily or less) have not been associated with an increased risk of myocardial infarction.

The lowest effective dose of NSAID should be prescribed for the shortest period of time to control symptoms, and the need for long-term treatment should be reviewed periodically.

All NSAIDs (including cyclo-oxygenase-2 selective inhibitors) are contra-indicated in children with active gastro-intestinal ulceration or bleeding. **Piroxicam** and **ketorolac** are contra-indicated in children with a history of gastro-intestinal bleeding, ulceration or perforation. Other non-selective NSAIDs are contra-indicated in children with a history of recurrent gastro-intestinal ulceration or haemorrhage (two or more distinct episodes), and in children with a history of gastro-intestinal bleeding or perforation related to previous NSAID therapy, see also NSAIDs and gastro-intestinal events below. For advice on the prophylaxis and treatment of NSAID-associated gastro-intestinal ulcers, see section 1.3. NSAIDs should also be used with caution in Crohn's disease or ulcerative colitis, as these conditions may be exacerbated.

For **interactions** of NSAIDs, see Appendix 1 (NSAIDs).

Hepatic impairment NSAIDs should be used with caution in children with hepatic impairment; there is an

increased risk of gastro-intestinal bleeding and fluid retention. NSAIDs should be avoided in severe liver disease; see also individual drugs.

Renal impairment NSAIDs should be avoided if possible or used with caution in children with renal impairment; the **lowest effective dose** should be used for the **shortest possible duration**, and renal function should be **monitored**. Sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure; deterioration in renal function has also been reported after topical use; see also individual drugs.

Pregnancy Most manufacturers advise avoiding NSAIDs during pregnancy or avoiding them unless the potential benefit outweighs risk. NSAIDs should be avoided during the third trimester because use is associated with a risk of closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension of the newborn. In addition, the onset of labour may be delayed and the duration may be increased.

See also individual monograph for etoricoxib.

Breast-feeding NSAIDs should be used with caution during breast-feeding; see also individual drugs.

Side-effects The side-effects of NSAIDs vary in severity and frequency. Gastro-intestinal disturbances including discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration may occur (see also notes below and Cautions above).

NSAIDs and gastro-intestinal events

All NSAIDs are associated with gastro-intestinal toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam (see also CHMP advice, p. 510) and ketorolac are associated with the highest risk; indometacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk). **Selective inhibitors of cyclooxygenase-2** are associated with a *lower risk* of serious upper gastro-intestinal side-effects than non-selective NSAIDs.

Children appear to tolerate NSAIDs better than adults and gastro-intestinal side-effects are less common although they do still occur and can be significant; use of gastro-protective drugs may be necessary (see also section 1.3).

Other side-effects include hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm), headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, hearing disturbances such as tinnitus, photosensitivity, and haematuria. Blood disorders have also occurred. Fluid retention may occur (rarely precipitating congestive heart failure); blood pressure may be raised.

Asthma

All NSAIDs have the potential to worsen asthma, either acutely or as a gradual worsening of symptoms; consider both prescribed NSAIDs and those that are purchased over the counter.

Renal failure may be provoked by NSAIDs, especially in patients with pre-existing renal impairment (**important**, see Renal impairment above). Rarely, papillary necrosis or interstitial fibrosis associated with NSAIDs can lead to renal failure. Hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare side-effects. Induction of or exacerbation of colitis or Crohn's disease has been reported. Aseptic meningitis has been reported rarely with NSAIDs—children with connective tissue disorders such as systemic lupus erythematosus may be especially susceptible.

Overdosage: see Emergency Treatment of Poisoning, p. 25.

DICLOFENAC POTASSIUM

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment avoid in severe impairment; see also notes above

Pregnancy see notes above

Breast-feeding amount in milk too small to be harmful; see also notes above

Side-effects see notes above

Licensed use *Voltarol*[®] *Rapid* not licensed for use in children under 14 years or in fever

Indications and dose

Rheumatic disease and musculoskeletal disorders

• By mouth

Child 14–18 years 75–100 mg daily in 2–3 divided doses

Postoperative pain

• By mouth

Child 9–14 years and body-weight over 35 kg up to 2 mg/kg (max. 100 mg) daily in 3 divided doses

Child 14–18 years 75–100 mg daily in 2–3 divided doses

Fever in ear, nose, or throat infection

• By mouth

Child 9–18 years and body-weight over 35 kg up to 2 mg/kg (max. 100 mg) daily in 3 divided doses

Diclofenac Potassium (Non-proprietary) ^(PoM)

Tablets, s/c, diclofenac potassium 25 mg, net price 28-tab pack = £3.23; 50 mg, 28-tab pack = £6.18.

Label: 21

¹*Voltarol*[®] *Rapid* (Novartis) ^(PoM)

Tablets, s/c, diclofenac potassium 25 mg (red), net price 30-tab pack = £3.46; 50 mg (brown), 30-tab pack = £6.62. Label: 21

- 12.5 mg tablets can be sold to the public for the treatment of headache, dental pain, period pain, rheumatic and muscular pain, backache and the symptoms of cold and flu (including fever), in patients aged over 14 years subject to max. single dose of 25 mg, max. daily dose of 75 mg for max. 3 days, and max. pack size of 18 × 12.5 mg

DICLOFENAC SODIUM

Cautions see notes above

Contra-indications see notes above; avoid suppositories in proctitis; avoid injections containing benzyl alcohol in neonates (see preparations below)
Intravenous use Additional contra-indications include concomitant NSAID or anticoagulant use (including low-dose heparins), history of haemorrhagic diathesis, history of confirmed or suspected cerebrovascular bleeding, operations with high risk of haemorrhage, history of asthma, moderate or severe renal impairment, hypovolaemia, dehydration

Hepatic impairment see notes above

Renal impairment avoid in severe impairment; see also Intravenous Use and notes above

Pregnancy see notes above

Breast-feeding amount in milk too small to be harmful; see also notes above

Side-effects see notes above; suppositories may cause rectal irritation; injection site reactions

Licensed use not licensed for use in children under 1 year; *suppositories* not licensed for use in children under 6 years except for use in children over 1 year for juvenile idiopathic arthritis; solid dose forms containing more than 25 mg not licensed for use in children; *injection* not licensed for use in children

Indications and dose

Inflammation and mild to moderate pain

- By mouth or by rectum

Child 6 months–18 years 0.3–1 mg/kg (max. 50 mg) 3 times daily

Postoperative pain

- By rectum

Child 6 months–18 years

Body-weight 8–12 kg 12.5 mg twice daily for max. 4 days

Body-weight over 12 kg 1 mg/kg (max. 50 mg) 3 times daily for max. 4 days

- By intravenous infusion or deep intramuscular injection into gluteal muscle

Child 2–18 years 0.3–1 mg/kg once or twice daily for max. 2 days (max. 150 mg daily)

Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis

- By mouth

Child 6 months–18 years 1.5–2.5 mg/kg (max. 75 mg) twice daily; total daily dose may alternatively be given in 3 divided doses

Administration for *intravenous infusion*, dilute 75 mg with 100–500 mL Glucose 5% or Sodium Chloride 0.9% (previously buffered with 0.5 mL Sodium Bicarbonate 8.4% solution or with 1 mL Sodium Bicarbonate 4.2% solution); give over 30–120 minutes

Diclofenac Sodium (Non-proprietary) (PoM)

Tablets, both e/c, diclofenac sodium 25 mg, net price 84-tab pack = £1.25; 50 mg, 84-tab pack = £1.10. Label: 5, 25

Brands include *Defenac*[®], *Dicloflex*[®], *Diclozip*[®], *Fenactol*[®], *Flamrase*[®]

Dispersible tablets, sugar-free, diclofenac sodium 10 mg

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Suppositories, diclofenac sodium 100 mg, net price 10 = £3.03

Brands include *Econac*[®]

Voltarol[®] (Novartis) (PoM)

Tablets, e/c, diclofenac sodium 25 mg (yellow), net price 84-tab pack = £2.94; 50 mg (brown), 84-tab pack = £4.57. Label: 5, 25

Dispersible tablets, sugar-free, pink, diclofenac, equivalent to diclofenac sodium 50 mg, net price 21-tab pack = £6.19. Label: 13, 21

Injection, diclofenac sodium 25 mg/mL, net price 3-mL amp = 83p

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2), propylene glycol

Suppositories, diclofenac sodium 12.5 mg, net price 10 = 58p; 25 mg, 10 = £1.03; 50 mg, 10 = £1.70; 100 mg, 10 = £3.03

Modified release

Diclomax SR[®] (Galen) (PoM)

Capsules, m/r, yellow, diclofenac sodium 75 mg, net price 56-cap pack = £9.69. Label: 21, 25

Dose

Pain and inflammation

- By mouth

Child 12–18 years 1 capsule 1–2 times daily

Diclomax Retard[®] (Galen) (PoM)

Capsules, m/r, diclofenac sodium 100 mg, net price 28-cap pack = £6.97. Label: 21, 25

Dose

Pain and inflammation

- By mouth

Child 12–18 years 1 capsule once daily

Motifene[®] 75 mg (Daiichi Sankyo) (PoM)

Capsules, e/c, m/r, diclofenac sodium 75 mg (enclosing e/c pellets containing diclofenac sodium 25 mg and m/r pellets containing diclofenac sodium 50 mg), net price 56-cap pack = £8.00. Label: 25

Excipients include propylene glycol (see Excipients, p. 2)

Dose

Pain and inflammation

- By mouth

Child 12–18 years 1 capsule 1–2 times daily

Voltarol[®] 75 mg SR (Novartis) (PoM)

Tablets, m/r, pink, diclofenac sodium 75 mg, net price 28-tab pack = £6.46; 56-tab pack = £12.92. Label: 21, 25

Dose

Pain and inflammation

- By mouth

Child 12–18 years 1 tablet 1–2 times daily

Note Other brands of modified-release tablets containing diclofenac sodium 75 mg include *Defenac*[®] SR, *Dexomon*[®] 75 SR, *Dicloflex*[®] 75 SR, *Fenactol*[®] 75 mg SR, *Flamatak*[®] 75 MR, *Flamrase*[®] SR, *Flexotard*[®] MR 75, *Rheumatac*[®] Retard 75, *Rhumalgan*[®] CR, *Slofenac*[®] SR, *Volsaid*[®] Retard 75

Voltarol[®] Retard (Novartis) (PoM)

Tablets, m/r, red, diclofenac sodium 100 mg, net price 28-tab pack = £9.47. Label: 21, 25

Dose

Pain and inflammation

- By mouth

Child 12–18 years 1 tablet once daily

Note Other brands of modified-release tablets containing diclofenac sodium 100 mg include *Defenac*[®] Retard, *Dexomon*[®] Retard 100, *Dicloflex*[®] Retard, *Fenactol*[®] Retard 100 mg, *Flamatak*[®] 100 MR, *Slofenac*[®] SR, *Volsaid*[®] Retard 100

ETORICOXIB

Cautions see notes above; also dehydration; monitor blood pressure before treatment, 2 weeks after initiation and periodically during treatment

Contra-indications see notes above; inflammatory bowel disease; uncontrolled hypertension (persistently above 140/90 mmHg)

Hepatic impairment max. 60 mg daily in mild impairment; max. 60 mg on alternate days or 30 mg once daily in moderate impairment; see also notes above

Renal impairment avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; see also notes above

Pregnancy manufacturer advises avoid (teratogenic in animal studies); see also notes above

Breast-feeding manufacturer advises avoid—present in milk in animal studies; see also notes above

Side-effects see notes above; also palpitation, fatigue, influenza-like symptoms, ecchymosis; *less commonly* dry mouth, taste disturbance, mouth ulcer, appetite and weight change, atrial fibrillation, transient ischaemic attack, chest pain, flushing, cough, dyspnoea, epistaxis, anxiety, mental acuity impaired, paraesthesia, electrolyte disturbance, myalgia and arthralgia; *very rarely* confusion and hallucinations

Indications and dose**Osteoarthritis**

• By mouth

Child 16–18 years 30 mg once daily, increased if necessary to 60 mg once daily

Rheumatoid arthritis and ankylosing spondylitis

• By mouth

Child 16–18 years 90 mg once daily

Acute gout

• By mouth

Child 16–18 years 120 mg once daily for max. 8 days

Arcoxia® (MSD) (PoM)

Tablets, f/c, etoricoxib 30 mg (blue-green), net price 28-tab pack = £13.99; 60 mg (dark green), 28-tab pack = £20.11; 90 mg (white), 28-tab pack = £22.96; 120 mg (pale green), 7-tab pack = £6.03, 28-tab pack = £24.11

IBUPROFEN

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment avoid in severe impairment; see also notes above

Pregnancy see notes above

Breast-feeding amount too small to be harmful, but some manufacturers advise avoid; see also notes above

Side-effects see notes above

Licensed use not licensed for use in children under 3 months or body-weight under 5 kg

Indications and dose

Mild to moderate pain, pain and inflammation of soft-tissue injuries, pyrexia with discomfort

• By mouth

Child 1–3 months 5 mg/kg 3–4 times daily

Child 3–6 months 50 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses

Child 6 months–1 year 50 mg 3–4 times daily; max. 30 mg/kg daily in 3–4 divided doses

Child 1–4 years 100 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses

Child 4–7 years 150 mg 3 times daily; max. 30 mg/kg daily in 3–4 divided doses

Child 7–10 years 200 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses

Child 10–12 years 300 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses

Child 12–18 years initially 300–400 mg 3–4 times daily; increased if necessary to max. 600 mg 4 times daily; maintenance dose of 200–400 mg 3 times daily may be adequate

Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis

• By mouth

Child 3 months–18 years 30–40 mg/kg (max. 2.4 g) daily in 3–4 divided doses; in systemic juvenile idiopathic arthritis up to 60 mg/kg (max. 2.4 g) daily [unlicensed] in 4–6 divided doses

Post-immunisation pyrexia in infants (see also p. 605)

• By mouth

Child 2–3 months 50 mg as a single dose repeated once after 6 hours if necessary

Closure of patent ductus arteriosus in neonates see section 2.14

¹Ibuprofen (Non-proprietary) (PoM)

Tablets, coated, ibuprofen 200 mg, net price 84-tab pack = £3.08; 400 mg, 84-tab pack = £3.15; 600 mg, 84-tab pack = £6.92. Label: 21

Brands include Arthrofen®, Ebufac®, Rimafen®

Dental prescribing on NHS Ibuprofen Tablets may be prescribed

Oral suspension, ibuprofen 100 mg/5 mL, net price 100 mL = £1.37, 150 mL = £2.11, 500 mL = £8.88. Label: 21

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Brands include Calprofen®, Feverfen®, Nurofen® for Children, Orbifen® for Children

Dental prescribing on NHS Ibuprofen Oral Suspension Sugar-free may be prescribed

Brufen® (Abbott Healthcare) (PoM)

Tablets, f/c, ibuprofen 200 mg, net price 100-tab pack = £3.92; 400 mg, 100-tab pack = £8.16; 600 mg, 100-tab pack = £12.24. Label: 21

Syrup, orange, ibuprofen 100 mg/5 mL, net price 500 mL (orange-flavoured) = £8.88. Label: 21

Granules, effervescent, ibuprofen 600 mg/sachet, net price 20–sachet pack = £6.80. Label: 13, 21
Contains sodium approx. 6.5 mmol/sachet

1. Can be sold to the public under certain circumstances

Modified release**Brufen Retard®** (Abbott Healthcare) (PoM)**Tablets**, m/r, ibuprofen 800 mg, net price 56-tab pack = £7.74. Label: 25, 27**Dose****Pain and inflammation**

- By mouth

Child 12–18 years 2 tablets daily as a single dose, preferably in the early evening, increased in severe cases to 3 tablets daily in 2 divided doses

INDOMETACIN

(Indomethacin)

Cautions see notes above; also epilepsy, psychiatric disturbances; during prolonged therapy ophthalmic and blood examinations particularly advisable; avoid rectal administration in proctitis and haemorrhoids

Skilled tasks Dizziness may affect performance of skilled tasks (e.g. driving)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment avoid in severe impairment; see also notes above

Pregnancy see notes above

Breast-feeding amount probably too small to be harmful—manufacturer advises avoid; see also notes above

Side-effects see notes above; *rarely* confusion, convulsions, psychiatric disturbances, syncope, blood disorders (particularly thrombocytopenia), hyperglycaemia, peripheral neuropathy, intestinal strictures; *also reported* hyperkalaemia; suppositories may cause rectal irritation and occasional bleeding

Licensed use not licensed for use in children

Indications and dose

Relief of pain and inflammation in rheumatic diseases including juvenile idiopathic arthritis (but see p. 504)

- By mouth

Child 1 month–18 years 0.5–1 mg/kg twice daily; higher doses may be used under specialist supervision

Closure of patent ductus arteriosus in premature babies section 2.14

Indometacin (Non-proprietary) (PoM)

Capsules, indometacin 25 mg, net price 28-cap pack = £1.17; 50 mg, 28-cap pack = £1.22. Label: 21, counselling, driving, see above

Suppositories, indometacin 100 mg, net price 10 = £17.61. Counselling, driving, see above

Suspension, indometacin 5 mg/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Modified release**Indometacin m/r preparations** (PoM)

Capsules, m/r, indometacin 75 mg. Label: 21, 25, counselling, driving, see above

Brands include Indolar SR®, Pardelprin®

MEFENAMIC ACID

Cautions see notes above; epilepsy; acute porphyria (section 9.8.2)

Contra-indications see notes above; inflammatory bowel disease

Hepatic impairment see notes above

Renal impairment avoid in severe impairment; see also notes above

Pregnancy see notes above

Breast-feeding amount too small to be harmful but manufacturer advises avoid; see also notes above

Side-effects see notes above; also diarrhoea or rashes (withdraw treatment), stomatitis; *less commonly* paraesthesia and fatigue; *rarely* hypotension, palpitation, glucose intolerance, thrombocytopenia, haemolytic anaemia (positive Coombs' test), and aplastic anaemia

Indications and dose

Acute pain including dysmenorrhoea, menorrhagia

- By mouth

Child 12–18 years 500 mg 3 times daily

Mefenamic Acid (Non-proprietary) (PoM)

Capsules, mefenamic acid 250 mg, net price 100 = £2.17. Label: 21

Tablets, mefenamic acid 500 mg, net price 28-tab pack = £1.66. Label: 21

Suspension, mefenamic acid 50 mg/5 mL, net price 125 mL = £79.98. Label: 21

Excipients include ethanol

Ponstan® (Chemidex) (PoM)

Capsules, blue/ivory, mefenamic acid 250 mg, net price 100-cap pack = £8.17. Label: 21

Forte tablets, yellow, mefenamic acid 500 mg, net price 100-tab pack = £15.72. Label: 21

MELOXICAM

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment avoid if estimated glomerular filtration rate less than 25 mL/minute/1.73 m²; see also notes above

Pregnancy see notes above

Breast-feeding present in milk in *animal* studies—manufacturer advises avoid; see also notes above

Side-effects see notes above

Licensed use not licensed for use in children under 16 years

Indications and dose

Relief of pain and inflammation in juvenile idiopathic arthritis and other musculoskeletal disorders in children intolerant to other NSAIDs

- By mouth

Child 12–18 years and body-weight under 50 kg 7.5 mg once daily

Child 12–18 years and body-weight over 50 kg 15 mg once daily

Meloxicam (Non-proprietary) (PoM)

Tablets, meloxicam 7.5 mg, net price 30-tab pack = £1.03; 15 mg, 30-tab pack = £1.13

NAPROXEN

Cautions see notes above; **interactions:** Appendix 1 (NSAIDs)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; see also notes above

Pregnancy see notes above

Breast-feeding amount too small to be harmful but manufacturer advises avoid; see also notes above

Side-effects see notes above

Licensed use not licensed for use in children under 5 years for juvenile idiopathic arthritis; not licensed for use in children under 16 years for musculoskeletal disorders or dysmenorrhoea

Indications and dose

Pain and inflammation in musculoskeletal disorders, dysmenorrhoea

- By mouth

Child 1 month–18 years 5 mg/kg twice daily (max. 1 g daily)

Juvenile idiopathic arthritis

- By mouth

Child 2–18 years 5–7.5 mg/kg twice daily (max. 1 g daily)

¹Naproxen (Non-proprietary) (PoM)

Tablets, naproxen 250 mg, net price 28-tab pack = £1.15; 500 mg, 28-tab pack = £1.82. Label: 21

Brands include *Arthrofen*[®]

Tablets, e/c, naproxen 250 mg, net price 56-tab pack = £2.71; 375 mg, 56-tab pack = £6.42; 500 mg, 56-tab pack = £5.02. Label: 5, 25

Suspension, naproxen 25 mg/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Naprosyn[®] (Roche) (PoM)

Tablets, yellow, scored, naproxen 250 mg, net price 56-tab pack = £4.29; 500 mg, 56-tab pack = £8.56. Label: 21

Tablets, e/c, (*Naprosyn EC*[®]), naproxen 250 mg, net price 56-tab pack = £4.29; 375 mg, 56-tab pack = £6.42; 500 mg, 56-tab pack = £8.56. Label: 5, 25

PIROXICAM

Cautions see notes above and CHMP advice below

Contra-indications inflammatory bowel disease; see also notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding amount too small to be harmful; see also notes above

Side-effects see notes above

Licensed use not licensed for use in children

Indications and dose

Relief of pain and inflammation in juvenile idiopathic arthritis

- By mouth

Child 6–18 years and body-weight under 15 kg 5 mg daily

1. Can be sold to the public for the treatment of primary dysmenorrhoea in women aged 15–50 years subject to max. single dose of 500 mg, max. daily dose of 750 mg for max. 3 days, and a max. pack size of 9 × 250 mg tablets

Child 6–18 years and body-weight 16–25 kg 10 mg daily

Child 6–18 years and body-weight 26–45 kg 15 mg daily

Child 6–18 years and body-weight over 46 kg 20 mg daily

CHMP advice

Piroxicam (June 2007)

The CHMP has recommended restrictions on the use of piroxicam because of the increased risk of gastro-intestinal side effects and serious skin reactions. The CHMP has advised that:

- piroxicam should be initiated only by physicians experienced in treating inflammatory or degenerative rheumatic diseases
- piroxicam should not be used as first-line treatment
- in adults, use of piroxicam should be limited to the symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis
- piroxicam dose should not exceed 20 mg daily
- piroxicam should no longer be used for the treatment of acute painful and inflammatory conditions
- treatment should be reviewed 2 weeks after initiating piroxicam, and periodically thereafter
- concomitant administration of a gastro-protective agent (section 1.3) should be considered

Note

Topical preparations containing piroxicam are not affected by these restrictions

Piroxicam (Non-proprietary) (PoM)

Capsules, piroxicam 10 mg, net price 56-cap pack = £6.78; 20 mg, 28-cap pack = £7.80. Label: 21

Dispersible tablets, piroxicam 10 mg, net price 56-tab pack = £9.96; 20 mg, 28-tab pack = £32.41. Label: 13, 21

Brexidol[®] (Chiesi) (PoM)

Tablets, yellow, scored, piroxicam (as betadex) 20 mg, net price 30-tab pack = £13.82. Label: 21

Feldene[®] (Pfizer) (PoM)

Capsules, piroxicam 10 mg (red/blue), net price 30-cap pack = £3.86; 20 mg (white), 30-cap pack = £7.71. Label: 21

Tablets, (*Feldene Melt*[®]), piroxicam 20 mg, net price 30-tab pack = £10.53. Label: 10, patient information leaflet, 21

Excipients include aspartame equivalent to phenylalanine 140 micrograms/tablet (section 9.4.1)

Note Tablets may be halved [unlicensed] to give 10-mg dose; tablet placed on tongue and allowed to dissolve or may be swallowed

10.1.2 Corticosteroids

10.1.2.1 Systemic corticosteroids

10.1.2.2 Local corticosteroid injections

10.1.2.1 Systemic corticosteroids

The general actions, uses, and cautions of corticosteroids are described in section 6.3. In children with rheumatic diseases corticosteroids should be reserved for specific indications (e.g. when other therapies are unsuccessful or while waiting for DMARDs to take effect) and should be used only under the supervision of a specialist.

Systemic corticosteroids may be considered for the management of juvenile idiopathic arthritis in systemic disease or when several joints are affected. Systemic corticosteroids may also be considered in severe, possibly life-threatening conditions such as systemic lupus erythematosus, systemic vasculitis, juvenile dermatomyositis, Behçet's disease, and polyarticular joint disease.

In severe conditions, short courses ('pulses') of high-dose intravenous methylprednisolone or a pulsed oral corticosteroid may be particularly effective for providing rapid relief, and has fewer long-term adverse effects than continuous treatment.

Corticosteroid doses should be reduced with care because of the possibility of relapse if the reduction is too rapid. If complete discontinuation of corticosteroids is not possible, consideration should be given to alternate-day (or alternate high-dose, low-dose) administration; on days when no corticosteroid is given, or a lower dose is given, an additional dose of a NSAID may be helpful. In some conditions, alternative treatment using an antimalarial or concomitant use of an immunosuppressant drug, such as azathioprine, methotrexate or cyclophosphamide may prove useful; in less severe conditions treatment with a NSAID alone may be adequate.

Administration of corticosteroids may result in suppression of growth and may affect the development of puberty. The risk of corticosteroid-induced osteoporosis should be considered for those on long-term corticosteroid treatment (section 6.6); corticosteroids may also increase the risk of osteopenia in those unable to exercise. For the disadvantages of corticosteroid treatment see section 6.3.2.

10.1.2.2 Local corticosteroid injections

Corticosteroids are injected locally for an anti-inflammatory effect. In inflammatory conditions of the joints, including juvenile idiopathic arthritis, they are given by *intra-articular injection* as monotherapy, or as an adjunct to long-term therapy to reduce swelling and deformity in one or a few joints. Aseptic precautions (e.g. a no-touch technique) are essential, as is a clinician skilled in the technique; infected areas should be avoided and general anaesthesia, or local anaesthesia, or conscious sedation should be used. Occasionally an acute inflammatory reaction develops after an intra-articular or soft-tissue injection of a corticosteroid. This may be a reaction to the microcrystalline suspension of the corticosteroid used, but must be distinguished from sepsis introduced into the injection site.

Triamcinolone hexacetonide [unlicensed] is preferred for intra-articular injection because it is almost insoluble and has a long-acting (depot) effect. Triamcinolone acetonide and methylprednisolone may also be considered for intra-articular injection into larger joints, whilst hydrocortisone acetate should be reserved for smaller joints or for soft-tissue injections. Intra-articular corticosteroid injections can cause flushing and, in adults, may affect the hyaline cartilage. Each joint should usually be treated no more than 3–4 times in one year.

A smaller amount of corticosteroid may also be injected directly into soft tissues for the relief of inflammation in conditions such as *tennis or golfer's elbow* or *compression neuropathies*, which occur rarely in children. In *tendinitis*, injections should be made into the tendon sheath and not directly into the tendon (due to the absence of a true

tendon sheath and a high risk of rupture, the Achilles tendon should not be injected).

Corticosteroid injections are also injected into soft tissues for the treatment of skin lesions (see section 13.4).

LOCAL CORTICOSTEROID INJECTIONS

Cautions see notes above and consult product literature; see also section 6.3.2

Contra-indications see notes above and consult product literature; avoid injections containing benzyl alcohol in neonates (see preparation below)

Side-effects see notes above and consult product literature

Licensed use triamcinolone acetonide not licensed for use in children under 6 years

Indications and dose

See under preparations

▲ Hydrocortisone acetate

Hydrocortistab® (AMCo) (PoM)

Injection (aqueous suspension), hydrocortisone acetate 25 mg/mL, net price 1-mL amp = £6.87

Dose

- By intra-articular injection

(for details consult product literature)

Child 1 month–12 years 5–30 mg according to size of child and joint

Child 12–18 years 5–50 mg according to size of child and joint

Note Where appropriate may be repeated at intervals of 21 days; not more than 3 joints should be treated on any one day

▲ Methylprednisolone acetate

Depo-Medrone® (Pharmacia) (PoM)

Injection (aqueous suspension), methylprednisolone acetate 40 mg/mL, net price 1-mL vial = £3.44; 2-mL vial = £6.18; 3-mL vial = £8.96

Depo-Medrone® with Lidocaine (Pharmacia) (PoM)

Injection (aqueous suspension), methylprednisolone acetate 40 mg, lidocaine hydrochloride 10 mg/mL, net price 1-mL vial = £3.94; 2-mL vial = £7.06

▲ Triamcinolone hexacetonide

Triamcinolone hexacetonide (Non-proprietary) (PoM)

Injection, various strengths available from 'special order' manufacturers or specialist importing companies, see, p. 840

Dose

- By intra-articular injection

(for details consult product literature)

Child 1–18 years for larger joints 1 mg/kg (usual max. 20 mg, but higher doses have been used); if appropriate repeat treatment for relapse

▲ Triamcinolone acetonide

Adcortyl® Intra-articular/Intradermal (Squibb) (PoM)

Injection (aqueous suspension), triamcinolone acetonide 10 mg/mL, net price 1-mL amp = 89p; 5-mL vial = £3.63

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Dose

- By intra-articular injection

(for details consult product literature)

Child 1–18 years for larger joints 2 mg/kg (max. 15 mg); for doses above 15 mg use *Kenalog®* Intra-articular/Intramuscular; if appropriate repeat treatment for relapse

Kenalog® Intra-articular/Intramuscular

(Squibb) (POM)

Injection (aqueous suspension), triamcinolone acetate 40 mg/mL, net price 1-mL vial = £1.49**Dose**

- By intra-articular injection

(for details consult product literature)

Child 1–18 years for larger joints 2 mg/kg (usual max. 40 mg, but higher doses have been used); if appropriate repeat treatment for relapse

10.1.3 Drugs that suppress the rheumatic disease process

Certain drugs, such as methotrexate, cytokine modulators, and sulfasalazine, are used to suppress the disease process in *juvenile idiopathic arthritis* (juvenile chronic arthritis); these drugs are known as disease-modifying antirheumatic drugs (DMARDs). In children, disease-modifying antirheumatic drugs should be used under specialist supervision.

Some children with juvenile idiopathic arthritis do not require disease-modifying antirheumatic drugs. Methotrexate is effective in juvenile idiopathic arthritis; sulfasalazine is an alternative but should be avoided in *systemic-onset juvenile idiopathic arthritis*. Gold and penicillamine are no longer used. For the role of cytokine modulators in *polyarticular juvenile idiopathic arthritis*, see p. 514.

Unlike NSAIDs, disease-modifying antirheumatic drugs can affect the progression of disease but they may require 3–6 months of treatment for a full therapeutic response. Response to a disease-modifying antirheumatic drug may allow the dose of the NSAID to be reduced.

Disease-modifying antirheumatic drugs can improve not only the symptoms of inflammatory joint disease but also extra-articular manifestations. They reduce the erythrocyte sedimentation rate and C-reactive protein.

Antimalarials

The antimalarial **hydroxychloroquine** is rarely used to treat juvenile idiopathic arthritis. Hydroxychloroquine can also be useful for systemic or discoid lupus erythematosus, particularly involving the skin and joints, and in sarcoidosis.

Retinopathy (see below) rarely occurs provided that the recommended doses are not exceeded.

Mepacrine is used on rare occasions to treat discoid lupus erythematosus [unlicensed].

Cautions Hydroxychloroquine should be used with caution in neurological disorders (especially in those with a history of epilepsy), in severe gastro-intestinal disorders, in G6PD deficiency (section 9.1.5), and in acute porphyria. Hydroxychloroquine may exacerbate psoriasis and aggravate myasthenia gravis. Concurrent use of hepatotoxic drugs should be avoided; other **interactions:** Appendix 1 (chloroquine and hydroxychloroquine).

Pregnancy It is not necessary to withdraw an antimalarial drug during pregnancy if the rheumatic disease

is well controlled; however, the manufacturer of hydroxychloroquine advises avoiding use.

Breast-feeding Hydroxychloroquine is present in breast milk leading to a risk of toxicity in infants—breast-feeding should be avoided when it is used to treat rheumatic disease.

Screening for ocular toxicity

Hydroxychloroquine is rarely associated with ocular toxicity. The British Society for Paediatric and Adolescent Rheumatology recommends that children should have their vision tested before long-term treatment with hydroxychloroquine and have an annual review of visual acuity. Children should be referred to an ophthalmologist if there is visual impairment, changes in visual acuity, or blurred vision. The Royal College of Ophthalmologists has recommended that a locally agreed protocol between the prescribing doctor and ophthalmologist be established to monitor the vision of these children.

Important

To avoid excessive dosage in obese children, the dose of hydroxychloroquine should be calculated on the basis of ideal body-weight; ocular toxicity is unlikely with doses under 5–6.5 mg/kg or max. 400 mg daily.

Side-effects The side-effects of hydroxychloroquine include gastro-intestinal disturbances, headache, and skin reactions (rashes, pruritus); those occurring less frequently include ECG changes, convulsions, visual changes, retinal damage (see above), keratopathy, ototoxicity, hair depigmentation, hair loss, and discoloration of skin, nails, and mucous membranes. Side-effects that occur rarely include blood disorders (including thrombocytopenia, agranulocytosis, and aplastic anaemia), mental changes (including emotional disturbances and psychosis), myopathy (including cardiomyopathy and neuromyopathy), acute generalised exanthematous pustulosis, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity, and hepatic damage; angioedema and bronchospasm have also been reported. **Important:** very toxic in overdosage—immediate advice from poisons centres essential (see also p. 28).

HYDROXYCHLOROQUINE SULFATE

Cautions see notes above

Hepatic impairment use with caution in moderate to severe impairment

Renal impairment manufacturer advises caution and monitoring of plasma-hydroxychloroquine concentration in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use *Plaquenil®* not licensed for use in children for dermatological conditions caused or aggravated by sunlight

Indications and dose

Juvenile idiopathic arthritis, systemic and discoid lupus erythematosus, dermatological conditions caused or aggravated by sunlight

- By mouth

Child 1 month–18 years based on ideal body-weight, 5–6.5 mg/kg (max. 400 mg) once daily

Hydroxychloroquine (Non-proprietary) (PoM)

Tablets, hydroxychloroquine sulfate 200 mg, net price 60-tab pack = £4.97. Label: 21, counselling, antacids (see below)

Brands include *Quinoric*®

Counselling Do not take antacids for at least 4 hours before or after hydroxychloroquine to reduce possible interference with hydroxychloroquine absorption

Plaquenil® (Sanofi-Aventis) (PoM)

Tablets, f/c, hydroxychloroquine sulfate 200 mg, net price 60-tab pack = £5.15. Label: 21, counselling, antacids (see below)

Counselling Do not take antacids for at least 4 hours before or after hydroxychloroquine to reduce possible interference with hydroxychloroquine absorption

Drugs affecting the immune response

Methotrexate, given as a once weekly dose, is the disease-modifying antirheumatic drug of choice in the treatment of juvenile idiopathic arthritis and also has a role in juvenile dermatomyositis, vasculitis, uveitis, systemic lupus erythematosus, localised scleroderma, and sarcoidosis; for these indications it is given by the subcutaneous, oral, or rarely, the intramuscular route. Absorption from intramuscular or subcutaneous routes may be more predictable than from the oral route; if the oral route is ineffective subcutaneous administration is generally preferred. Regular full blood counts (including differential white cell count and platelet count), renal and liver function tests are required. Folic acid may reduce mucosal or gastro-intestinal side-effects of methotrexate. The dosage regimen for folic acid has not been established—in children over 2 years a dose of 5 mg weekly (unlicensed indication), may be given on a different day from the methotrexate.

Azathioprine may be used in children for vasculitis which has failed to respond to other treatments, for the management of severe cases of *systemic lupus erythematosus* and other connective tissue disorders, in conjunction with corticosteroids for patients with severe or progressive renal disease, and in cases of *polymyositis* which are resistant to corticosteroids. Azathioprine has a corticosteroid-sparing effect in patients whose corticosteroid requirements are excessive.

Ciclosporin is rarely used in juvenile idiopathic arthritis, connective tissue diseases, vasculitis, and uveitis; it may be considered if the condition has failed to respond to other treatments.

AZATHIOPRINE

Cautions section 8.2.1

Contra-indications section 8.2.1

Hepatic impairment section 8.2.1

Renal impairment section 8.2.1

Pregnancy section 8.2.1

Breast-feeding section 8.2.1

Side-effects section 8.2.1

Indications and dose

Systemic lupus erythematosus, vasculitis, autoimmune conditions usually when corticosteroid therapy alone has proved inadequate see also notes above

- By mouth

Child 1 month–18 years initially 1 mg/kg daily, adjusted according to response to max. 3 mg/kg daily (consider withdrawal if no improvement within 3 months)

Inflammatory bowel disease section 1.5.3

Transplantation rejection section 8.2.1

Preparations

Section 8.2.1

METHOTREXATE

Cautions section 8.1.3; see advice below (blood count, gastro-intestinal, liver, and pulmonary toxicity); extreme caution in blood disorders (avoid if severe); risk of accumulation in pleural effusion or ascites—drain before treatment; full blood count and liver function tests before starting treatment repeated fortnightly for at least the first 4 weeks and at this frequency after any change in dose until therapy stabilised, thereafter monthly; renal function tests before starting treatment and then regularly during treatment; children or their carers should report all symptoms and signs suggestive of infection, especially sore throat; treatment with folic acid (as calcium folinate, section 8.1) may be required in acute toxicity; check immunity to varicella-zoster and consider vaccination (section 14.4) before initiating therapy; acute porphyria (section 9.8.2); **interactions**: see below and Appendix 1 (methotrexate)

Blood count Bone marrow suppression can occur abruptly; factors likely to increase toxicity include renal impairment and concomitant use with another anti-folate drug (e.g. trimethoprim). A clinically significant drop in white cell count or platelet count calls for immediate withdrawal of methotrexate and introduction of supportive therapy

Gastro-intestinal toxicity Withdraw treatment if stomatitis develops—may be first sign of gastro-intestinal toxicity

Liver toxicity Persistent 2-fold rise in liver transaminases may necessitate dose reduction or rarely discontinuation; abrupt withdrawal should be avoided as this can lead to disease flare

Pulmonary toxicity Acute pulmonary toxicity is rare in children treated for juvenile idiopathic arthritis, but children and carers should seek medical attention if dyspnoea, cough or fever develops; discontinue if pneumonia suspected.

NSAIDs Children and carers should be advised to avoid self-medication with over-the-counter ibuprofen

Contra-indications see Cautions above; also active infection and immunodeficiency syndromes

Hepatic impairment avoid—dose-related toxicity; see also Cautions above

Renal impairment section 8.1.3

Pregnancy section 8.1.3

Breast-feeding section 8.1.3

Side-effects section 8.1.3; chronic pulmonary fibrosis; blood dyscrasias (including fatalities); liver cirrhosis

Licensed use *Metoject*® is licensed for use in children over 3 years for polyarticular forms of juvenile idiopathic arthritis; other preparations not licensed for use in children for non-malignant conditions

Indications and dose

Juvenile idiopathic arthritis, juvenile dermatomyositis, vasculitis, uveitis, systemic lupus erythematosus, localised scleroderma, sarcoidosis

- By mouth, subcutaneous injection, or intramuscular injection

Child 1 month–18 years 10–15 mg/m² once weekly initially, increased if necessary to max. 25 mg/m² once weekly

Safe Practice

Note that the above dose is a **weekly** dose. To avoid error with low-dose methotrexate, it is recommended that:

- the child or their carer is carefully advised of the **dose** and **frequency** and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the child or their carer is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).

Severe Crohn's disease section 1.5.3

Malignant disease section 8.1.3

Psoriasis section 13.5.3

Methotrexate (Non-proprietary) (PoM)

Tablets, yellow, methotrexate 2.5 mg, net price 24-tab pack = £3.16, 28-tab pack = £2.60. Counselling, dose, NSAIDs

Brands include *Maxtrex*[®]

Tablets, yellow, methotrexate 10 mg, net price 100-tab pack = £37.06. Counselling, dose, NSAIDs

Suspension, various strengths available from 'special-order' manufacturers or specialist importing companies, see p. 840

Parenteral preparations

See also section 8.1.3

Metotect[®] (Medac) (PoM)

Injection, prefilled syringe, methotrexate (as disodium salt) 50 mg/mL, net price 0.15 mL (7.5 mg) = £14.85, 0.2 mL (10 mg) = £15.29, 0.3 mL (15 mg) = £16.57, 0.4 mL (20 mg) = £17.84, 0.5 mL (25 mg) = £18.48, 0.6 mL (30 mg) = £18.95

Cytokine modulators

Cytokine modulators should be used under specialist supervision.

Adalimumab, etanercept, and infliximab inhibit the activity of tumour necrosis factor alpha (TNF- α). Adalimumab can be used for the management of active polyarticular juvenile idiopathic arthritis. Etanercept is licensed for the treatment of the following subtypes of juvenile idiopathic arthritis: polyarticular juvenile idiopathic arthritis in children who have had an inadequate response to methotrexate or who cannot tolerate it, oligoarthritis in children who have had an inadequate

response to methotrexate or who cannot tolerate it, psoriatic arthritis in children over 12 years who have had an inadequate response to methotrexate or cannot tolerate it, and enthesitis-related arthritis in children over 12 years who have had an inadequate response to conventional therapy or cannot tolerate it. Infliximab has been used in refractory polyarticular juvenile idiopathic arthritis (unlicensed indication) when other treatments, such as etanercept, have failed.

The *Scottish Medicines Consortium* (p. 3) has advised (January 2013) that etanercept (*Enbrel*[®]) is accepted for restricted use within NHS Scotland for the treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to or are intolerant of methotrexate, psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to or are intolerant of methotrexate, and enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to or are intolerant of conventional therapy. It is further restricted to use within specialist rheumatology services (including those working within the network for paediatric rheumatology).

NICE guidance**Etanercept for the treatment of juvenile idiopathic arthritis (March 2002)**

Etanercept is recommended in children aged 4–17 years with active polyarticular-course juvenile idiopathic arthritis who have not responded adequately to methotrexate or who are intolerant of it. Etanercept should be used under specialist supervision according to the guidelines of the British Society for Paediatric and Adolescent Rheumatology [previously the British Paediatric Rheumatology Group]. Etanercept should be withdrawn if severe side-effects develop or if there is no response after 6 months or if the initial response is not maintained. A decision to continue therapy beyond 2 years should be based on disease activity and clinical effectiveness in individual cases.

Prescribers of etanercept should register consenting patients with the Biologics Registry of the British Society for Paediatric and Adolescent Rheumatology.

www.nice.org.uk/TA35

Side-effects Adalimumab, etanercept, and infliximab have been associated with infections, sometimes severe, including tuberculosis, septicæmia, and hepatitis B reactivation. Other side-effects include nausea, abdominal pain, worsening heart failure, hypersensitivity reactions, fever, headache, depression, antibody formation (including lupus erythematosus-like syndrome), pruritus, injection-site reactions, and blood disorders (including anaemia, leucopenia, thrombocytopenia, pancytopenia, aplastic anaemia).

Abatacept prevents the full activation of T-lymphocytes; it can be used for the management of active polyarticular juvenile idiopathic arthritis. Abatacept is not recommended for use in combination with TNF inhibitors.

The *Scottish Medicines Consortium* (p. 3) has advised (October 2011) that abatacept (*Orencia*[®]) is accepted for restricted use within NHS Scotland for the treatment of moderate to severe active polyarticular juvenile idio-

pathic arthritis in accordance with the licensed indications, when used within specialist rheumatology services (including those working within the network for paediatric rheumatology).

Canakinumab inhibits the activity of interleukin-1 beta (IL-1 β) and is licensed for the treatment of active systemic juvenile idiopathic arthritis in children over 2 years, when there has been an inadequate response to NSAIDs and systemic corticosteroids.

Tocilizumab antagonises the actions of interleukin-6; it can be used for the management of active systemic juvenile idiopathic arthritis when there has been an inadequate response to NSAIDs and systemic corticosteroids and polyarticular juvenile idiopathic arthritis when there has been an inadequate response to methotrexate. Tocilizumab can be used in combination with methotrexate, or as monotherapy if methotrexate is not tolerated or is contra-indicated (see also NICE guidance below). Tocilizumab is not recommended for use with other cytokine modulators.

NICE guidance

Tocilizumab for the treatment of systemic juvenile idiopathic arthritis (December 2011)

Tocilizumab is recommended for the treatment of systemic juvenile idiopathic arthritis in children aged over 2 years who have not responded adequately to NSAIDs, systemic corticosteroids and methotrexate, if the manufacturer makes tocilizumab available with the discount agreed as part of the patient access scheme.

Tocilizumab is not recommended for the treatment of systemic juvenile idiopathic arthritis in children whose disease continues to respond to methotrexate or who have not been treated with methotrexate.

Children currently receiving tocilizumab for systemic juvenile idiopathic arthritis who do not meet these criteria should have the option to continue treatment until it is considered appropriate to stop.

www.nice.org.uk/TA238

ABATACEPT

Cautions predisposition to infection (screen for latent tuberculosis and viral hepatitis); do not initiate until active infections are controlled; children should be brought up to date with current immunisation schedule (section 14.1) before initiating therapy; progressive multifocal leucoencephalopathy—discontinue treatment if neurological symptoms present; **interactions:** Appendix 1 (abatacept)

Contra-indications severe infection (see also Cautions)

Pregnancy manufacturer advises avoid unless essential—effective contraception required during treatment and for 14 weeks after last dose

Breast-feeding present in milk in animal studies—manufacturer advises avoid breast-feeding during treatment and for 14 weeks after last dose

Side-effects abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, stomatitis, flushing, hypertension, cough, dizziness, fatigue, headache, paraesthesia, infection, leucopenia, pain in extremities, conjunctivitis; *less commonly* gastritis, tachycardia, bradycardia, palpitation, hypotension, bronchospasm, dyspnoea, hyperhidrosis, weight gain, depression,

anxiety, sleep disorder, menstrual disturbances, basal and squamous cell carcinoma, skin papilloma, thrombocytopenia, arthralgia, visual disturbance, dry eye, bruising, alopecia, dry skin, psoriasis; *also reported* lymphoma, lung cancer

Indications and dose

Moderate to severe active polyarticular juvenile idiopathic arthritis (in combination with methotrexate) in children who have not responded adequately to other disease-modifying anti-rheumatic drugs (including at least one tumour necrosis factor (TNF) inhibitor)

• By intravenous infusion

Child 6–17 years

Body-weight less than 75 kg 10 mg/kg, repeated 2 weeks and 4 weeks after initial infusion, then every 4 weeks

Body-weight 75–100 kg 750 mg, repeated 2 weeks and 4 weeks after initial infusion, then every 4 weeks

Body-weight over 100 kg 1 g, repeated 2 weeks and 4 weeks after initial infusion, then every 4 weeks

Note Review treatment if no response within 6 months

Administration for *intravenous infusion*, reconstitute each vial with 10 mL water for injections using the silicone-free syringe provided; dilute requisite dose in Sodium Chloride 0.9% to 100 mL (using the same silicone-free syringe); give over 30 minutes through a low protein-binding filter (pore size 0.2–1.2 micron)

Orencia® (Bristol-Myers Squibb) (PoM)

Intravenous infusion, powder for reconstitution, abatacept, net price 250-mg vial = £302.40

Electrolytes Na⁺ <0.5 mmol/vial

ADALIMUMAB

Cautions predisposition to infection; monitor for infection before, during, and for 4 months after treatment (see also Tuberculosis below); do not initiate until active infections are controlled; discontinue if new serious infection develops; hepatitis B virus—monitor for active infection; children should be brought up to date with current immunisation schedule (section 14.1) before initiating therapy; mild heart failure (discontinue if symptoms develop or worsen—avoid in moderate or severe heart failure); demyelinating disorders (risk of exacerbation); history or development of malignancy; monitor for non-melanoma skin cancer before and during treatment, especially in children with history of PUVA treatment for psoriasis or extensive immunosuppressant therapy; **interactions:** Appendix 1 (adalimumab)

Tuberculosis Children should be evaluated for tuberculosis before treatment. Active tuberculosis should be treated with standard treatment (section 5.1.9) for at least 2 months before starting adalimumab. Children who have previously received adequate treatment for tuberculosis can start adalimumab but should be monitored every 3 months for possible recurrence. In those without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting adalimumab. In children at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with adalimumab. Children and their carers should be advised to seek medical attention if symptoms suggestive of

tuberculosis (e.g. persistent cough, weight loss, and fever) develop

Blood disorders Children and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop

Contra-indications severe infection (see also Cautions)

Pregnancy avoid; manufacturer advises effective contraception required during treatment and for at least 5 months after last dose

Breast-feeding avoid; manufacturer advises avoid for at least 5 months after last dose

Side-effects see under Cytokine Modulators, p. 514 and Cautions above; also vomiting, dyspepsia, gastrointestinal haemorrhage, dizziness, hyperlipidaemia, hypertension, oedema, flushing, chest pain, tachycardia, cough, dyspnoea, mood changes, sleep disturbances, anxiety, paraesthesia, haematuria, renal impairment, benign tumours, skin cancer, electrolyte disturbances, hyperuricaemia, dehydration, musculoskeletal pain, eye disorders, rash, dermatitis, onycholysis, impaired healing; *less commonly* dysphagia, pancreatitis, cholelithiasis, hepatic steatosis, cholecystitis, arrhythmias, vascular occlusion, aortic aneurysm, interstitial lung disease, pneumonitis, tremor, erectile dysfunction, nocturia, malignancy (including solid tumours and lymphoma), rhabdomyolysis, hearing loss, tinnitus; *rarely* autoimmune hepatitis, myocardial infarction, demyelinating disorders; *also reported* pulmonary embolism, pleural effusion, sarcoidosis, Stevens-Johnson syndrome, cutaneous vasculitis, new onset or worsening psoriasis

Indications and dose

Active polyarticular juvenile idiopathic arthritis (in combination with methotrexate or alone if methotrexate inappropriate) in children who have not responded adequately to one or more disease-modifying antirheumatic drug

- By subcutaneous injection

Child 2–4 years 24 mg/m² (max. 20 mg) on alternate weeks; review treatment if no response within 12 weeks

Child 4–13 years 24 mg/m² (max. 40 mg) on alternate weeks; review treatment if no response within 12 weeks

Child 13–18 years 40 mg on alternate weeks; review treatment if no response within 12 weeks

Inflammatory bowel disease section 1.5.3

Humira® (AbbVie) (POM)

Injection, adalimumab, net price 40-mg prefilled pen or prefilled syringe = £352.14; 40 mg/0.8-mL vial = £352.14. Label: 10, alert card, counselling, tuberculosis and blood disorders

CANAKINUMAB

Cautions section 8.2.4

Contra-indications section 8.2.4

Hepatic impairment section 8.2.4

Renal impairment section 8.2.4

Pregnancy section 8.2.4

Breast-feeding section 8.2.4

Side-effects section 8.2.4; also abdominal pain, arthralgia, musculoskeletal pain, rhinitis

Indications and dose

Active systemic juvenile idiopathic arthritis (in combination with methotrexate or alone) in children who have had an inadequate response to NSAIDs and systemic corticosteroids

- By subcutaneous injection

Child 2–18 years and body-weight over 7.5 kg 4 mg/kg (max. 300 mg) once every 4 weeks

Cryopyrin-associated periodic syndromes section 8.2.4

Preparations

Section 8.2.4

ETANERCEPT

Cautions predisposition to infection (avoid if predisposition to septicaemia); significant exposure to herpes zoster virus—interrupt treatment and consider varicella-zoster immunoglobulin; hepatitis B virus—monitor for active infection; monitor for worsening hepatitis C infection; children should be brought up to date with current immunisation schedule (section 14.1) before initiating therapy; heart failure (risk of exacerbation); history or increased risk of demyelinating disorders; history or development of malignancy; monitor for skin cancer before and during treatment particularly in those at risk (including children with psoriasis or a history of PUVA treatment); history of blood disorders; diabetes mellitus; **interactions:** Appendix 1 (etanercept)

Tuberculosis Children should be evaluated for tuberculosis before treatment. Active tuberculosis should be treated with standard treatment (section 5.1.9) for at least 2 months before starting etanercept. Children who have previously received adequate treatment for tuberculosis can start etanercept but should be monitored every 3 months for possible recurrence. In those without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting etanercept. In children at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with etanercept. Children and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop

Blood disorders Children and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop

Contra-indications active infection; avoid injections containing benzyl alcohol in neonates (see preparations below)

Hepatic impairment use with caution in moderate to severe alcoholic hepatitis

Pregnancy avoid—limited information available; manufacturer advises effective contraception required during treatment and for 3 weeks after last dose

Breast-feeding manufacturer advises avoid—present in milk in animal studies

Side-effects see under Cytokine Modulators, p. 514; also *less commonly* interstitial lung disease, skin cancer, uveitis, rash, new onset or worsening psoriasis; *rarely* demyelinating disorders, seizures, lymphoma, Stevens-Johnson syndrome, vasculitis; *very rarely* toxic epidermal necrolysis; *also reported* appendicitis, gastritis, oesophagitis, inflammatory bowel disease, vomiting, diabetes mellitus, malignancy (including

solid tumours and leukaemia), macrophage activation syndrome, and cutaneous ulcer

Indications and dose

Juvenile idiopathic arthritis (see also notes above)

• By subcutaneous injection

Child 2–17 years 400 micrograms/kg (max. 25 mg) twice weekly, with an interval of 3–4 days between doses or 800 micrograms/kg (max. 50 mg) once weekly; consider discontinuation if no response after 4 months

Severe plaque psoriasis section 13.5.3

Enbrel® (Pfizer) (PoM)

Injection, powder for reconstitution, etanercept, net price 25-mg vial (with solvent) = £89.38. Label: 10, alert card, counselling, tuberculosis and blood disorders

Paediatric injection, powder for reconstitution, etanercept, net price 10-mg vial (with solvent) = £35.75; 25-mg vial (with solvent) = £89.38. Label: 10, alert card, counselling, tuberculosis and blood disorders

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Injection, etanercept, net price 25-mg prefilled syringe = £89.38; 50-mg prefilled pen or prefilled syringe = £178.75. Label: 10, alert card, counselling, tuberculosis and blood disorders

TOCILIZUMAB

Cautions predisposition to infection or history of recurrent or chronic infection; interrupt treatment if serious infection occurs; history of intestinal ulceration or diverticulitis; monitor hepatic transaminases; monitor neutrophil and platelet counts; low platelet or absolute neutrophil count (discontinue if absolute neutrophil count less than 0.5×10^9 /litre or platelet count less than 50×10^3 /microlitre); monitor lipid profile 4–8 weeks after starting treatment and then as indicated; monitor for demyelinating disorders; **interactions:** Appendix 1 (tocilizumab)

Tuberculosis Children should be evaluated for tuberculosis before treatment. Children with latent tuberculosis should be treated with standard therapy (section 5.1.9) before starting tocilizumab

Counselling Children and their carers should be advised to seek immediate medical attention if symptoms of infection occur, or if symptoms of diverticular perforation such as abdominal pain, haemorrhage, or fever accompanying change in bowel habits occur

Contra-indications severe active infection (see also Cautions) do not initiate if absolute neutrophil count less than 2×10^9 /litre (see also Cautions)

Hepatic impairment manufacturer advises caution, consult product literature

Renal impairment manufacturer advises monitor renal function closely in moderate or severe impairment

Pregnancy manufacturer advises avoid unless essential (toxicity in animal studies); effective contraception required during and for 3 months after treatment

Breast-feeding manufacturer advises use only if potential benefit outweighs risk —no information available

Side-effects nausea, diarrhoea, raised hepatic transaminases, hypercholesterolaemia, headache, infection (including upper respiratory-tract infection),

thrombocytopenia, neutropenia, infusion-related reactions; antibody formation also reported

Indications and dose

Active systemic juvenile idiopathic arthritis (in combination with methotrexate or alone if methotrexate inappropriate) in children who have had an inadequate response to NSAIDs and systemic corticosteroids

• By intravenous infusion

Child 2–18 years

Body-weight less than 30 kg 12 mg/kg once every 2 weeks; review treatment if no improvement within 6 weeks

Body-weight over 30 kg 8 mg/kg once every 2 weeks; review treatment if no improvement within 6 weeks

Polyarticular juvenile idiopathic arthritis (in combination with methotrexate or alone if methotrexate inappropriate) in children who have had an inadequate response to methotrexate

• By intravenous infusion

Child 2–18 years

Body-weight less than 30 kg 10 mg/kg once every 4 weeks; review treatment if no improvement within 12 weeks

Body-weight over 30 kg 8 mg/kg once every 4 weeks; review treatment if no improvement within 12 weeks

Administration for intravenous infusion; body-weight less than 30 kg, dilute requisite dose to a volume of 50 mL with Sodium chloride 0.9% and give over 1 hour; body-weight over 30 kg, dilute requisite dose to a volume of 100 mL with Sodium chloride 0.9% and give over 1 hour

RoActemra® (Roche) (PoM)

Concentrate for intravenous injection, tocilizumab 20 mg/mL, net price 4 mL (80-mg vial) = £102.40, 10 mL (200-mg) vial = £256.00, 20 mL (400-mg vial) = £512.00. Alert card, counselling, see above

Sulfasalazine

Sulfasalazine has a beneficial effect in suppressing the inflammatory activity associated with some forms of juvenile idiopathic arthritis; it is generally not used in systemic-onset disease. Sulfasalazine may cause haematological abnormalities including leucopenia, neutropenia, and thrombocytopenia and close monitoring of full blood counts (including differential white cell count and platelet count) is necessary initially, and at monthly intervals during the first 3 months (liver-function tests also being performed at monthly intervals for the first 3 months). Although the manufacturer recommends renal function tests, evidence of practical value is unsatisfactory. For use of sulfasalazine also see section 1.5.1, aminosalicilates.

SULFASALAZINE (Sulphasalazine)

Cautions see section 1.5.1 and notes above

Contra-indications see section 1.5.1

Hepatic impairment section 1.5.1

Renal impairment section 1.5.1

Pregnancy section 1.5.1

Breast-feeding section 1.5.1

Side-effects see section 1.5.1 and notes above

Licensed use not licensed for use in children for juvenile idiopathic arthritis

Indications and dose

Juvenile idiopathic arthritis (see also notes above)

• By mouth

Child 2–18 years initially 5 mg/kg twice daily for 1 week, then 10 mg/kg twice daily for 1 week, then 20 mg/kg twice daily for 1 week, maintenance dose 20–25 mg/kg twice daily; **Child 2–12 years** max. 2 g daily, **Child 12–18 years** max. 3 g daily

Preparations

Section 1.5.1

10.1.4 Gout and cytotoxic-induced hyperuricaemia

This section is not included in *BNF for Children*. For the role of allopurinol and rasburicase in the prophylaxis of hyperuricaemia associated with cancer chemotherapy and in enzyme disorders causing increased serum urate, see section 8.1. The management of gout in adolescents requires specialist supervision.

10.1.5 Other drugs for rheumatic diseases

Classification not used in *BNF for Children*.

10.2 Drugs used in neuromuscular disorders

10.2.1 Drugs that enhance neuromuscular transmission

10.2.2 Skeletal muscle relaxants

10.2.1 Drugs that enhance neuromuscular transmission

Anticholinesterases are used as first-line treatment in *ocular myasthenia gravis* and as an adjunct to immunosuppressant therapy for *generalised myasthenia gravis*.

Corticosteroids are used when anticholinesterases do not control symptoms completely. A second-line immunosuppressant such as azathioprine is frequently used to reduce the dose of corticosteroid.

Plasmapheresis or infusion of intravenous immunoglobulin [unlicensed indication] may induce temporary remission in severe relapses, particularly where bulbar or respiratory function is compromised or before thymectomy.

Anticholinesterases

Anticholinesterase drugs enhance neuromuscular transmission in voluntary and involuntary muscle in myasthenia gravis. They prolong the action of acetylcholine by inhibiting the action of the enzyme acetylcholinesterase. Excessive dosage of these drugs can impair neuromuscular transmission and precipitate cholinergic

crises by causing a depolarising block. This may be difficult to distinguish from a worsening myasthenic state.

Muscarinic side-effects of anticholinesterases include increased sweating, increased salivary and gastric secretions, increased gastro-intestinal and uterine motility, and bradycardia. These parasympathomimetic effects are antagonised by atropine.

Edrophonium has a very brief action and it is therefore used mainly for the diagnosis of myasthenia gravis. However, such testing should be performed only by those experienced in its use; other means of establishing the diagnosis are available. A single test-dose usually causes substantial improvement in muscle power (lasting about 5 minutes) in patients with the disease (if respiration already impaired, *only* in conjunction with someone skilled at intubation).

Edrophonium can also be used to determine whether a patient with myasthenia is receiving inadequate or excessive treatment with cholinergic drugs. If treatment is excessive an injection of edrophonium will either have no effect or will intensify symptoms (if respiration already impaired, *give only* in conjunction with someone skilled at intubation). Conversely, transient improvement may be seen if the patient is being inadequately treated. The test is best performed just before the next dose of anticholinesterase.

Neostigmine produces a therapeutic effect for up to 4 hours. Its pronounced muscarinic action is a disadvantage, and simultaneous administration of an antimuscarinic drug such as atropine or propantheline may be required to prevent colic, excessive salivation, or diarrhoea. In severe disease neostigmine can be given every 2 hours. In infants, neostigmine by either subcutaneous or intramuscular injection is preferred for the short-term management of myasthenia.

Pyridostigmine is less powerful and slower in action than neostigmine but it has a longer duration of action. It is preferable to neostigmine because of its smoother action and the need for less frequent dosage. It is particularly preferred in patients whose muscles are weak on waking. It has a comparatively mild gastro-intestinal effect but an antimuscarinic drug may still be required. It is inadvisable to use excessive doses because acetylcholine receptor down regulation may occur. Immunosuppressant therapy may be considered if high doses of pyridostigmine are needed. Neostigmine and pyridostigmine should be given to neonates 30 minutes before feeds to improve suckling.

Neostigmine and edrophonium are also used to reverse the actions of the non-depolarising neuromuscular blocking drugs (section 15.1.6).

NEOSTIGMINE

Cautions asthma (*extreme* caution), bradycardia, arrhythmias, recent myocardial infarction, epilepsy, hypotension, parkinsonism, vagotonia, peptic ulceration, hyperthyroidism; atropine or other antidote to muscarinic effects may be necessary (particularly when neostigmine is given by injection), but not given routinely because it may mask signs of overdosage; **interactions:** Appendix 1 (parasympathomimetics)

Contra-indications intestinal or urinary obstruction

Renal impairment may need dose reduction

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding amount probably too small to be harmful

Side-effects nausea, vomiting, increased salivation, diarrhoea, abdominal cramps (more marked with higher doses); signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defaecation and micturition, miosis, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, and weakness eventually leading to fasciculation and paralysis

Indications and dose

Treatment of myasthenia gravis

- By mouth (as neostigmine bromide)

Neonate initially 1–2 mg, then 1–5 mg every 4 hours, give 30 minutes before feeds

Child up to 6 years initially 7.5 mg repeated at suitable intervals throughout the day, total daily dose 15–90 mg

Child 6–12 years initially 15 mg repeated at suitable intervals throughout the day, total daily dose 15–90 mg

Child 12–18 years initially 15–30 mg repeated at suitable intervals throughout the day, total daily dose 75–300 mg (but max. most can tolerate is 180 mg daily)

- By subcutaneous or intramuscular injection (as neostigmine metilsulfate)

Neonate 150 micrograms/kg every 6–8 hours, 30 minutes before feeds, increased to max. 300 micrograms/kg every 4 hours, if necessary [unlicensed]

Child 1 month–12 years 200–500 micrograms repeated at suitable intervals throughout the day

Child 12–18 years 1–2.5 mg repeated at suitable intervals throughout the day

Neostigmine (Non-proprietary) ^(PoM)

Tablets, scored, neostigmine bromide 15 mg, net price 140 = £88.31

Injection

Section 15.1.6

EDROPHONIUM CHLORIDE

Cautions see under Neostigmine; have resuscitation facilities; *extreme* caution in respiratory distress (see notes above) and in asthma

Note Severe cholinergic reactions can be counteracted by injection of atropine sulfate (which should always be available)

Contra-indications see under Neostigmine

Pregnancy see under Neostigmine

Breast-feeding see under Neostigmine

Side-effects see under Neostigmine

Indications and dose

Diagnostic test for myasthenia gravis

- By intravenous injection

Child 1 month–12 years 20 micrograms/kg followed after 30 seconds (if no adverse reaction has occurred) by 80 micrograms/kg

Child 12–18 years 2 mg followed after 30 seconds (if no adverse reaction has occurred) by 8 mg

Detection of overdosage or underdosage of cholinergic drugs

- By intravenous injection

Child 1 month–12 years 20 micrograms/kg (preferably just before next dose of anticholinesterase, see notes above)

Child 12–18 years 2 mg (preferably just before next dose of anticholinesterase, see notes above)

Edrophonium (Non-proprietary) ^(PoM)

Injection, edrophonium chloride 10 mg/mL, net price 1-mL amp = £19.50

PYRIDOSTIGMINE BROMIDE

Cautions see under Neostigmine; weaker muscarinic action

Contra-indications see under Neostigmine

Renal impairment reduce dose; excreted by kidney

Pregnancy see under Neostigmine

Breast-feeding see under Neostigmine

Side-effects see under Neostigmine

Indications and dose

Treatment of myasthenia gravis

- By mouth

Neonate initially 1–1.5 mg/kg, increased gradually to max. 10 mg, repeated throughout the day, give 30–60 minutes before feeds

Child 1 month–12 years initially 1–1.5 mg/kg/day, increased gradually to 7 mg/kg/day in 6 divided doses; usual total daily dose 30–360 mg

Child 12–18 years 30–120 mg, repeated throughout the day; usual total daily dose 300–600 mg (but consider immunosuppressant therapy if total daily dose exceeds 360 mg, down-regulation of acetylcholine receptors possible if total daily dose exceeds 450 mg; see notes above)

Mestinon[®] (Meda) ^(PoM)

Tablets, scored, pyridostigmine bromide 60 mg, net price 200 = £45.57

Immunosuppressant therapy

A course of **corticosteroids** (section 6.3) is an established treatment in severe cases of myasthenia gravis and may be particularly useful when antibodies to the acetylcholine receptor are present in high titre. Short courses of high-dose ('pulsed') methylprednisolone followed by maintenance therapy with oral corticosteroids may also be useful.

Corticosteroid treatment is usually initiated under specialist supervision. For disadvantages of corticosteroid treatment, see section 6.3.2. Transient but very serious worsening of symptoms can occur in the first 2–3 weeks, especially if the corticosteroid is started at a high dose. Once remission has occurred (usually after 2–6 months), the dose of prednisolone should be reduced slowly to the minimum effective dose.

10.2.2 Skeletal muscle relaxants

The drugs described below are used for the relief of chronic muscle spasm or spasticity associated with neurological damage; they are not indicated for spasm associated with minor injuries. They act principally on the central nervous system with the exception of dantrolene, which has a peripheral site of action. They differ in action from the muscle relaxants used in anaesthesia (section 15.1.5), which block transmission at the neuromuscular junction.

The underlying cause of spasticity should be treated and any aggravating factors (e.g. pressure sores, infection) remedied. Skeletal muscle relaxants are effective in most forms of spasticity except the rare alpha variety. The major disadvantage of treatment with these drugs is that reduction in muscle tone can cause a loss of splinting action of the spastic leg and trunk muscles and sometimes lead to an increase in disability.

Dantrolene acts directly on skeletal muscle and produces fewer central adverse effects. It is generally used in resistant cases. The dose should be increased slowly.

Baclofen inhibits transmission at spinal level and also depresses the central nervous system. The dose should be increased slowly to avoid the major side-effects of sedation and muscular hypotonia (other adverse events are uncommon).

Diazepam has undoubted efficacy in some children. Sedation and occasionally extensor hypotonus are disadvantages. Other benzodiazepines also have muscle-relaxant properties.

BACLOFEN

Cautions psychiatric illness; respiratory impairment; epilepsy; history of peptic ulcer (avoid oral route in active peptic ulceration); diabetes; hypertonic bladder sphincter; avoid abrupt withdrawal (risk of hyperactive state, may exacerbate spasticity, and precipitate autonomic dysfunction including hyperthermia, psychiatric reactions and convulsions, see also under Withdrawal below); **interactions:** Appendix 1 (muscle relaxants)

Withdrawal Serious side-effects can occur on abrupt withdrawal; to minimise risk, discontinue by gradual dose reduction over at least 1–2 weeks (longer if symptoms occur)

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Specific cautions for intrathecal treatment coagulation disorders; previous spinal fusion procedure; malnutrition (increased risk of post-surgical complications)

Contra-indications

Specific contra-indications for intrathecal treatment local or systemic infection

Hepatic impairment manufacturer advises use by mouth with caution

Renal impairment risk of toxicity—use smaller oral doses and if necessary increase dosage interval; if estimated glomerular filtration rate less than 15 mL/minute/1.73 m² use by mouth only if potential benefit outweighs risk; excreted by kidney

Pregnancy manufacturer advises use only if potential benefit outweighs risk (toxicity in animal studies)

Breast-feeding present in milk—amount probably too small to be harmful

Side-effects gastro-intestinal disturbances, dry mouth; hypotension, respiratory or cardiovascular

depression; sedation, drowsiness, confusion, dizziness, ataxia, hallucinations, nightmares, headache, euphoria, insomnia, depression, anxiety, agitation, tremor; seizure; urinary disturbances; myalgia; visual disorders; rash, hyperhidrosis; *rarely* taste disturbances, abdominal pain, changes in hepatic function, paraesthesia, erectile dysfunction, dysarthria; *very rarely* hypothermia

Indications and dose

Chronic severe spasticity of voluntary muscle

• By mouth

Child under 18 years initially 300 micrograms/kg daily in 4 divided doses, increased gradually at weekly intervals until satisfactory response; usual maintenance dose of 0.75–2 mg/kg daily in divided doses; **Child up to 8 years** max. total daily dose 40 mg/day, **Child 8–18 years** max. total daily dose 60 mg/day; review treatment if no benefit within 6 weeks of achieving maximum dose

Severe chronic spasticity of cerebral or spinal origin unresponsive to oral antispastic drugs (or oral therapy not tolerated)—specialist use only

• By intrathecal injection

Child 4–18 years initial *test* dose 25–50 micrograms over at least 1 minute via catheter or lumbar puncture, increased in 25-microgram steps (not more often than every 24 hours) to max. 100 micrograms to determine initial maintenance dose *then dose-titration phase*, most often using infusion pump (implanted into chest wall or abdominal wall tissues) to establish maintenance dose retaining some spasticity to avoid sensation of paralysis; initial *maintenance dose* 25–200 micrograms daily, adjusted according to response

Safe Practice

Consult intrathecal injection product literature for details on dose testing and titration—important to monitor patients closely in appropriately equipped and staffed environment during screening and immediately after pump implantation. Resuscitation equipment must be available for immediate use. Treatment with continuous pump-administered intrathecal baclofen should be initiated within 3 months of a satisfactory response to intrathecal baclofen testing.

Baclofen (Non-proprietary) (PoM)

Tablets, baclofen 10 mg, net price 84-tab pack = £1.67. Label: 2, 8, 21

Oral solution, baclofen 5 mg/5 mL, net price 300 mL = £4.48. Label: 2, 8, 21

Brands include *Lyfless*® (sugar-free)

Intrathecal injection, baclofen 50 micrograms/mL, net price 1-mL amp (for test dose) = £2.19; 500 micrograms/mL, 20-mL amp (for use with implantable pump) = £48.62; 2 mg/mL, 5-mL amp (for use with implantable pump) = £48.62

Lioreal® (Novartis) (PoM)

Tablets, scored, baclofen 10 mg, net price 100-tab pack = £12.38. Label: 2, 8, 21

Excipients include gluten

Liquid, sugar-free, raspberry-flavoured, baclofen 5 mg/5 mL, net price 300 mL = £8.59. Label: 2, 8, 21

Intrathecal injection, baclofen 50 micrograms/mL, net price 1-mL amp (for test dose) = £2.63; 500 micrograms/mL, 20-mL amp (for use with implantable pump) = £58.34; 2 mg/mL, 5-mL amp (for use with implantable pump) = £58.34

DANTROLENE SODIUM

Cautions impaired cardiac and pulmonary function; therapeutic effect may take a few weeks to develop—discontinue if no response within 6–8 weeks; **interactions:** Appendix 1 (muscle relaxants)

Hepatotoxicity Potentially life-threatening hepatotoxicity reported, usually if doses greater than 400 mg daily used, in females, if history of liver disorders, or concomitant use of hepatotoxic drugs; test liver function before and at intervals during therapy—discontinue if abnormal liver function tests or symptoms of liver disorder (counselling, see below); re-introduce only if complete reversal of hepatotoxicity

Counselling Children and their carers should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop

Skilled tasks Drowsiness may affect performance of skilled tasks (eg, driving); effects of alcohol enhanced

Contra-indications acute muscle spasm; avoid when spasticity is useful, for example, locomotion

Hepatic impairment avoid—may cause severe liver damage; injection may be used in an emergency for malignant hyperthermia

Pregnancy avoid use in chronic spasticity—embryotoxic in animal studies

Breast-feeding present in milk—manufacturer advises avoid use in chronic spasticity

Side-effects diarrhoea (withdraw if severe, discontinue treatment if recurs on re-introduction), nausea, vomiting, anorexia, hepatotoxicity (see above), abdominal pain; pericarditis; pleural effusion, respiratory depression; headache, drowsiness, dizziness, asthenia, fatigue, seizures, fever, chills; speech and visual disturbances; rash; *less commonly* dysphagia, constipation, exacerbation of cardiac insufficiency, tachycardia, erratic blood pressure, dyspnoea, depression, confusion, nervousness, insomnia, increased urinary frequency, urinary incontinence or retention, haematuria, crystalluria, and increased sweating

Licensed use not licensed for use in children

Indications and dose

Chronic severe spasticity of voluntary muscle

• By mouth

Child 5–12 years initially 500 micrograms/kg once daily; after 7 days increase to 500 micrograms/kg/dose 3 times daily; every 7 days increase by further 500 micrograms/kg/dose until satisfactory response; max. 2 mg/kg 3–4 times daily (max. total daily dose 400 mg)

Child 12–18 years initially 25 mg once daily; increase to 3 times daily after 7 days; every 7 days increase by further 500 micrograms/kg/dose until satisfactory response; max. 2 mg/kg 3–4 times daily (max. total daily dose 400 mg)

Malignant hyperthermia section 15.1.8

Dantrium® (SpePharm) (PoM)

Capsules, orange/brown, dantrolene sodium 25 mg, net price 100 = £16.87; 100 mg, 100 = £43.07. Label: 2, counselling, driving, hepatotoxicity

DIAZEPAM

Cautions section 4.8.2

Contra-indications section 4.8.2

Hepatic impairment section 4.8.2

Renal impairment section 4.8.2

Pregnancy section 4.8.2

Breast-feeding section 4.8.2

Side-effects section 4.8.2; also hypotonia

Indications and dose

Muscle spasm in cerebral spasticity or in post-operative skeletal muscle spasm

• By mouth

Child 1–12 months initially 250 microgram/kg twice daily

Child 1–5 years initially 2.5 mg twice daily

Child 5–12 years initially 5 mg twice daily

Child 12–18 years initially 10 mg twice daily; max. total daily dose 40 mg

Tetanus

• By intravenous injection

Child 1 month–18 years 100–300 micrograms/kg repeated every 1–4 hours

• By intravenous infusion (or by nasoduodenal tube)

Child 1 month–18 years 3–10 mg/kg over 24 hours, adjusted according to response

Status epilepticus section 4.8.2

Febrile convulsions section 4.8.3

Administration for *continuous intravenous infusion* of diazepam emulsion, dilute to a concentration of max. 400 micrograms/mL with Glucose 5% or 10%; max. 6 hours between addition and completion of infusion; diazepam adsorbed by plastics of infusion bags and giving sets

For *continuous intravenous infusion* of diazepam solution, dilute to a concentration of max. 50 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; diazepam adsorbed by plastics of infusion bags and giving sets

Diazepam (Non-proprietary) (CD-1)

Tablets, diazepam 2 mg, net price 28 = 80p; 5 mg, 28 = 83p; 10 mg, 28 = 92p. Label: 2 or 19

Brands include Rimapam[®], Tensium[®]

Dental prescribing on NHS Diazepam Tablets may be prescribed

Oral solution, diazepam 2 mg/5 mL, net price 100 mL = £6.08. Label: 2 or 19

Brands include Ditalar[®]

Dental prescribing on NHS Diazepam Oral Solution 2 mg/5 mL may be prescribed

Strong oral solution, diazepam 5 mg/5 mL, net price 100-mL pack = £6.38. Label: 2 or 19

Brands include Ditalar[®]

Parenteral preparations

Section 4.8.2

10.3 Drugs for the treatment of soft-tissue disorders and topical pain relief

10.3.1 Enzymes

10.3.2 Rubefacients, topical NSAIDs, capsaicin, and poultices

Extravasation

Local guidelines for the management of extravasation should be followed where they exist or specialist advice sought.

Extravasation injury follows leakage of drugs or intravenous fluids from the veins or inadvertent administration into the subcutaneous or subdermal tissue. It must be dealt with **promptly** to prevent tissue necrosis.

Acidic or alkaline preparations and those with an osmolality greater than that of plasma can cause extravasation injury; excipients including alcohol and polyethylene glycol have also been implicated. Cytotoxic drugs commonly cause extravasation injury. Very young children are at increased risk. Those receiving anticoagulants are more likely to lose blood into surrounding tissues if extravasation occurs, while those receiving sedatives or analgesics may not notice the early signs or symptoms of extravasation.

Prevention of extravasation Precautions should be taken to avoid extravasation; ideally, drugs likely to cause extravasation injury should be given through a central line and children receiving repeated doses of hazardous drugs peripherally should have the cannula resited at regular intervals. Attention should be paid to the manufacturers' recommendations for administration. Placing a glyceryl trinitrate patch or using glyceryl trinitrate ointment distal to the cannula may improve the patency of the vessel in children with small veins or in those whose veins are prone to collapse.

Children or their carers should be asked to report any pain or burning at the site of injection immediately.

Management of extravasation If extravasation is suspected the infusion should be stopped immediately but the cannula should not be removed until after an attempt has been made to aspirate the area (through the cannula) in order to remove as much of the drug as possible. Aspiration is sometimes possible if the extravasation presents with a raised bleb or blister at the injection site and is surrounded by hardened tissue, but it is often unsuccessful if the tissue is soft or soggy. **Corticosteroids** are usually given to treat inflammation, although there is little evidence to support their use in extravasation. Hydrocortisone or dexamethasone (section 6.3.2) can be given either locally by subcutaneous injection or intravenously at a site distant from the injury. **Antihistamines** (section 3.4.1) and **analgesics** (section 4.7) may be required for symptom relief.

The management of extravasation beyond these measures is not well standardised and calls for specialist advice. Treatment depends on the nature of the offending substance; one approach is to localise and neutralise the substance whereas another is to spread and dilute it. The first method may be appropriate following extravasation of vesicant drugs and involves administration

of an antidote (if available) and the application of cold compresses 3–4 times a day (consult specialist literature for details of specific antidotes). Spreading and diluting the offending substance involves infiltrating the area with physiological saline, applying warm compresses, elevating the affected limb, and administering hyaluronidase (section 10.3.1). A saline flush-out technique (involving flushing the subcutaneous tissue with physiological saline) may be effective but requires specialist advice. Hyaluronidase should **not** be administered following extravasation of vesicant drugs (unless it is either specifically indicated or used in the saline flush-out technique).

10.3.1 Enzymes

Hyaluronidase is used for the management of extravasation. For preparations, see *BNF section 10.3.1*.

10.3.2 Rubefacients, topical NSAIDs, capsaicin, and poultices

Classification not used in *BNF for Children*.

11 Eye

11.1	Administration of drugs to the eye	523
11.2	Control of microbial contamination	524
11.3	Anti-infective eye preparations	524
11.3.1	Antibacterials	524
11.3.2	Antifungals	527
11.3.3	Antivirals	527
11.4	Corticosteroids and other anti-inflammatory preparations	527
11.4.1	Corticosteroids	527
11.4.2	Other anti-inflammatory preparations	528
11.5	Mydriatics and cycloplegics	530
11.6	Treatment of glaucoma	531
11.7	Local anaesthetics	535
11.8	Miscellaneous ophthalmic preparations	536
11.8.1	Tear deficiency, ocular lubricants, and astringents	536
11.8.2	Ocular diagnostic and peri-operative preparations	539
11.9	Contact lenses	540

11.1 Administration of drugs to the eye

Drugs are most commonly administered to the eye by topical application as eye drops or eye ointments. When a higher drug concentration is required within the eye, a local injection may be necessary, see Other Preparations, below.

Eye-drop dispenser devices are available to aid the instillation of eye drops from plastic bottles and some are prescribable on the NHS (consult Drug Tariff—see Appliances and Reagents, p. 829 for links to online Drug Tariffs). Product-specific devices may be supplied by manufacturers—contact individual manufacturers for further information. They are particularly useful for children in whom normal application is difficult, for the visually impaired, or otherwise physically limited patients.

Eye drops and eye ointments Eye drops are generally instilled into the pocket formed by gently pulling down the lower eyelid and keeping the eye closed for as long as possible after application; in neonates and infants it may be more appropriate to administer the drop in the inner angle of the open eye. One drop is all that is needed; instillation of more than one drop at a time should be discouraged because it may increase systemic side-effects. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it.

When two different eye-drop preparations are used at the same time of day, dilution and overflow can occur when one immediately follows the other. The carer or child should therefore leave an interval of at least 5 minutes between the two; the interval should be extended when eye drops with a prolonged contact time, such as gels and suspensions, are used. Eye ointment should be applied after drops. Both drops and ointment can cause transient blurred vision; children should be warned, where appropriate, not to perform skilled tasks (e.g. cycling or driving) until vision is clear.

Systemic effects may arise from absorption of drugs into the general circulation from conjunctival vessels or from the nasal mucosa after the excess preparation has drained down through the tear ducts. The extent of systemic absorption following ocular administration is highly variable; nasal drainage of drugs is associated with eye drops much more often than with eye ointments. Pressure on the lacrimal punctum for at least a minute after applying eye drops reduces nasolacrimal drainage and therefore decreases systemic absorption from the nasal mucosa.

For warnings relating to eye drops and contact lenses, see section 11.9.

Eye lotions These are solutions for the irrigation of the conjunctival sac. They act mechanically to flush out irritants or foreign bodies as a first-aid treatment. Sterile sodium chloride 0.9% solution (section 11.8.1) is usually used. Clean water will suffice in an emergency.

Other preparations Subconjunctival injection may be used to administer anti-infective drugs, mydriatics, or corticosteroids for conditions not responding to topical therapy; intracameral and intravitreal routes can also be used to administer certain drugs. These injections should only be used under specialist supervision.

Drugs such as antimicrobials and corticosteroids may be administered systemically to treat an eye condition.

Preservatives and sensitisers Information on preservatives and substances identified as skin sensitisers (section 13.1.3) is provided under Excipients statements in preparation entries. Very rarely, cases of corneal calcification have been reported with the use of phosphate-containing eye drops in patients with significantly damaged corneas—consult product literature for further information.

11.2 Control of microbial contamination

Preparations for the eye should be sterile when issued. Care should be taken to avoid contamination of the contents during use.

Eye drops in multiple-application containers for *domiliary* use should not be used for more than 4 weeks after first opening (unless otherwise stated by the manufacturer).

Multiple application eye drops for use in *hospital wards* are normally discarded 1 week after first opening—local practice may vary. Individual containers should be provided for each child. A separate container should be supplied for each eye only if there are special concerns about contamination. Containers used before an eye operation should be discarded at the time of the operation and fresh containers supplied postoperatively. A fresh supply should also be provided upon discharge from hospital; in specialist ophthalmology units it may be acceptable to issue containers that have been dispensed to the child on the day of discharge.

In *out-patient departments* single-application containers should be used; if multiple-application containers are used, they should be discarded after single patient use within one clinical session.

In *eye surgery* single-application containers should be used if possible; if a multiple-application container is used, it should be discarded after single use. Preparations used during intra-ocular procedures and others that may penetrate into the anterior chamber must be isotonic and without preservatives and buffered if necessary to a neutral pH. Specially formulated fluids should be used for intra-ocular surgery; intravenous infusion preparations are not usually suitable for this purpose (Hartmann's solution may be used in some ocular surgery). For all surgical procedures, a previously unopened container is used for each child.

11.3 Anti-infective eye preparations

11.3.1 Antibacterials

11.3.2 Antifungals

11.3.3 Antivirals

Eye infections Most acute superficial eye infections can be treated topically. Blepharitis and conjunctivitis are often caused by staphylococci; keratitis and endophthalmitis may be bacterial, viral, or fungal.

Bacterial *blepharitis* is treated by lid hygiene and application of antibacterial eye drops to the conjunctival sac or to the lid margins. Systemic treatment may be required and may be necessary for 3 months or longer.

Most cases of acute bacterial conjunctivitis are self-limiting; where treatment is appropriate, antibacterial eye drops or an eye ointment are used. A poor response might indicate viral or allergic conjunctivitis or antibiotic resistance.

Corneal ulcer and *keratitis* require specialist treatment, usually under inpatient care, and may call for intensive topical, subconjunctival, or systemic administration of antimicrobials.

Endophthalmitis is a medical emergency which also calls for specialist management and requires intravitreal administration of antimicrobials; concomitant systemic treatment is required in some cases. Surgical intervention, such as vitrectomy, is sometimes indicated.

For reference to the treatment of *crab lice of the eyelashes*, see section 13.10.4

11.3.1 Antibacterials

Bacterial eye infections are generally treated topically with eye drops and eye ointments; systemic treatment is sometimes appropriate in blepharitis.

Chloramphenicol has a broad spectrum of activity and is the drug of choice for *superficial eye infections*. Chloramphenicol eye drops are well tolerated and the recommendation that chloramphenicol eye drops should be avoided because of an increased risk of aplastic anaemia is not well founded.

Other antibacterials with a broad spectrum of activity include the quinolones, **ciprofloxacin**, **levofloxacin**, **moxifloxacin**, and **ofloxacin**; the aminoglycosides, **gentamicin** and **tobramycin** are also active against a wide variety of bacteria. Gentamicin, tobramycin, quinolones (except moxifloxacin), and **polymyxin B** are effective for infections caused by *Pseudomonas aeruginosa*.

Ciprofloxacin eye drops are licensed for *corneal ulcers*; intensive application (especially in the first 2 days) is required throughout the day and night.

Azithromycin eye drops are licensed for trachomatous conjunctivitis caused by *Chlamydia trachomatis* and for purulent bacterial conjunctivitis. *Trachoma*, which results from chronic infection with *Chlamydia trachomatis*, can be treated with azithromycin by mouth [unlicensed indication].

Fusidic acid is useful for staphylococcal infections.

Propamidine isetionate is of little value in bacterial infections but is used by specialists to treat the rare, but

potentially sight-threatening, condition of *acanthamoeba keratitis* (see also section 11.9).

Other antibacterial eye drops may be prepared aseptically in a specialist manufacturing unit from material supplied for injection, see section 11.8.

Neonates Antibacterial eye drops are used to treat acute bacterial conjunctivitis in neonates (ophthalmia neonatorum); where possible the causative micro-organism should be identified. **Chloramphenicol** eye drops are used to treat mild conjunctivitis; more serious infections also require a systemic antibacterial. Failure to respond to initial treatment requires further investigation; chlamydial infection is one of the most frequent causes of neonatal conjunctivitis and should be considered.

Azithromycin eye drops are licensed to treat trachomatous conjunctivitis caused by *Chlamydia trachomatis* and purulent bacterial conjunctivitis in neonates. However, as there is a risk of simultaneous infection at other sites in neonates and children under 3 months presenting with conjunctivitis caused by *Chlamydia trachomatis*, systemic treatment with oral **erythromycin** is required, see section 5.1.

Gonococcal eye infections are treated with a single-dose of parenteral **cefotaxime** or **ceftriaxone**. **Gentamicin** eye drops together with appropriate systemic antibacterials are used in the treatment of *pseudomonal eye infections*; high-strength gentamicin eye drops (1.5%) [unlicensed] are available for severe infections.

With corticosteroids Many antibacterial preparations also incorporate a corticosteroid but such mixtures should **not** be used unless a patient is under close specialist supervision. In particular they should not be prescribed for undiagnosed 'red eye' which is sometimes caused by the herpes simplex virus and may be difficult to diagnose (section 11.4).

Administration Frequency of application depends on the severity of the infection and the potential for irreversible ocular damage; antibacterial eye preparations are usually administered as follows:

- *Eye drops*, apply 1 drop at least every 2 hours in severe infection then reduce frequency as infection is controlled and continue for 48 hours after healing. For less severe infection 3–4 times daily is generally sufficient;
- *Eye ointment*, apply *either* at night (if eye drops used during the day) or 3–4 times daily (if eye ointment used alone).

AZITHROMYCIN DIHYDRATE

Side-effects ocular discomfort (including pruritus and burning), blurred vision; *less commonly* eyelid eczema, eyelid erythema, eyelid oedema, conjunctival hyperaemia, keratitis

Indications and dose

Purulent bacterial conjunctivitis

Apply twice daily for 3 days; review if no improvement after 3 days

Trachomatous conjunctivitis (see also Neonates above)

Apply twice daily for 3 days; review if no improvement after 3 days

Single use

Azyter® (Spectrum Thea) (PoM)

Eye drops, azithromycin dihydrate 1.5%, net price 6 × 0.25 g = £6.99

CHLORAMPHENICOL

Pregnancy avoid unless essential—no information on topical use but risk of neonatal 'grey-baby syndrome' with oral use in third trimester

Breast-feeding avoid unless essential—*theoretical* risk of bone-marrow toxicity

Side-effects transient stinging; see also notes above

Indications and dose

See notes above

Chloramphenicol (Non-proprietary) (PoM)

Eye drops, chloramphenicol 0.5%, net price 10 mL = £1.44

Eye ointment, chloramphenicol 1%, net price 4 g = £1.63

Note Chloramphenicol 0.5% eye drops (max. pack size 10 mL) and 1% eye ointment (max. pack size 4 g) can be sold to the public for treatment of acute bacterial conjunctivitis in children over 2 years; max. duration of treatment 5 days

Chloromycetin® (AMCo) (PoM)

Redidrops (= eye drops), chloramphenicol 0.5%, net price 5 mL = £1.65; 10 mL = 90p

Excipients include phenylmercuric acetate

Ophthalmic ointment (= eye ointment), chloramphenicol 1%, net price 4 g = £1.08

Single use

Minims® **Chloramphenicol** (Bausch & Lomb) (PoM)

Eye drops, chloramphenicol 0.5%, net price 20 × 0.5 mL = £10.53

CIPROFLOXACIN

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises caution

Side-effects taste disturbance, ocular discomfort, ocular hyperaemia, corneal deposits (reversible after completion of treatment); *less commonly* nausea, headache, keratopathy, corneal infiltrates, corneal staining, photophobia, blurred vision, eyelid disorders (including oedema, exfoliation, erythema), eye irritation (including pain, swelling, pruritus, dryness), increased lacrimation, conjunctival hyperaemia; *rarely* diarrhoea, abdominal pain, dizziness, keratitis, corneal disorders including corneal epithelium defect, eye hypoesthesia, asthenopia, diplopia, ear pain, paranasal sinus hypersecretion, rhinitis, dermatitis

Licensed use eye ointment not licensed for use in children under 1 year

Indications and dose

Superficial bacterial infections

Apply eye drops 4 times daily; in severe infection apply every 2 hours during waking hours for 2 days, then 4 times daily; max. duration of treatment 21 days

Apply 1.25 cm eye ointment 3 times daily for 2 days, then twice daily for 5 days

Corneal ulcer

Apply eye drops throughout day and night, day 1 apply every 15 minutes for 6 hours then every 30 minutes, day 2 apply every hour, days 3–14 apply every 4 hours; max. duration of treatment 21 days
 Apply eye ointment throughout day and night; apply 1.25 cm ointment every 1–2 hours for 2 days then every 4 hours for next 12 days

Ciloxan® (Alcon) (PoM)

Ophthalmic solution (= eye drops), ciprofloxacin (as hydrochloride) 0.3%, net price 5 mL = £4.70

Excipients include benzalkonium chloride

Eye ointment, ciprofloxacin (as hydrochloride) 0.3%, net price 3.5 g = £5.22

FUSIDIC ACID**Indications and dose**

See notes above and under preparation below

Fucithalmic® (LEO) (PoM)

Eye drops, m/r, fusidic acid 1% in gel basis (liquified on contact with eye), net price 5 g = £2.69

Excipients include benzalkonium chloride, disodium edetate

Dose

Apply twice daily

GENTAMICIN**Indications and dose**

See notes above

Genticin® (AMCo) (PoM)

Drops (for ear or eye), gentamicin (as sulfate) 0.3%, net price 10 mL = £2.13

Excipients include benzalkonium chloride

Gentamicin (Non-proprietary) (PoM)

Eye drops, gentamicin 1.5%, 10 mL, available as a manufactured special from Moorfields Eye Hospital, see also 'special-order' manufacturers or specialist importing companies, p. 840

LEVOFLOXACIN

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises use only if potential benefit outweighs risk

Side-effects ocular burning, visual disturbances; *less commonly* headache, ocular discomfort (including itching, pain, and dryness), conjunctival follicles, lid oedema, lid erythema, photophobia, rhinitis

Indications and dose

Local treatment of infections (see also notes above)

Child 1–18 years apply every 2 hours (max. 8 times daily) for the first 2 days, then 4 times daily for 3 days

Oftaquin® (Kestrel Ophthalmics) (PoM)

Eye drops, levofloxacin 0.5%, net price 5 mL = £6.95

Excipients include benzalkonium chloride

Unit dose eye drops, levofloxacin 0.5%, net price 30 × 0.5-mL single use units = £17.95

MOXIFLOXACIN

Cautions not recommended for neonates

Side-effects taste disturbances, ocular discomfort (including pain, irritation, and dryness), hyperaemia; *less commonly* vomiting, headache, paraesthesia, corneal disorders (including keratitis, erosion, and staining), conjunctival haemorrhage, eyelid erythema, visual disturbances, nasal discomfort, pharyngolaryngeal pain; *also reported* nausea, palpitation, dyspnoea, dizziness, raised intra-ocular pressure, photophobia, rash, pruritus

Indications and dose

Local treatment of infections (see also notes above)

Child 1 month–18 years apply 3 times daily (continue treatment for 2–3 days after infection improves; review if no improvement within 5 days)

Moxivig® (Alcon) (PoM)

Eye drops, moxifloxacin (as hydrochloride) 0.5%, net price 5 mL = £9.80

OFLOXACIN

Cautions corneal ulcer or epithelial defect (risk of corneal perforation)

Pregnancy manufacturer advises use only if benefit outweighs risk; systemic quinolones have caused arthropathy in *animal* studies

Breast-feeding manufacturer advises avoid

Side-effects ocular discomfort and irritation; *also reported* facial oedema, keratitis, visual disturbances, photophobia, increased lacrimation, ocular oedema, dry eyes, ocular hyperaemia

Indications and dose

Local treatment of infections (see also notes above)

Child 1–18 years apply every 2–4 hours for the first 2 days, then reduce frequency to 4 times daily (max. 10 days treatment)

Exocin® (Allergan) (PoM)

Ophthalmic solution (= eye drops), ofloxacin 0.3%, net price 5 mL = £2.17

Excipients include benzalkonium chloride

PROPAMIDINE ISETIONATE

Pregnancy manufacturer advises avoid unless essential—no information available

Breast-feeding manufacturer advises avoid unless essential—no information available

Side-effects eye pain and irritation

Indications and dose

See under preparations below

Brolene® (Sanofi-Aventis)

Eye drops, propamidine isetionate 0.1%, net price 10 mL = £2.80

Excipients include benzalkonium chloride

Dose

Local treatment of infections (but see notes above)

Apply up to 4 times daily

Eye ointment, dibrompropamide isetonate 0.15%, net price 5 g = £2.92

Dose

Local treatment of infections (but see notes above)

Apply 1–2 times daily

Golden Eye® (Typharm)

Eye drops, propamide isetonate 0.1%, net price 10 mL = £3.26

Excipients include benzalkonium chloride

Dose

Local treatment of infections (but see section 11.3.1)

Apply up to 4 times daily

Eye ointment, dibrompropamide isetonate 0.15%, net price 5 g = £3.49

Dose

Local treatment of infections (but see section 11.3.1)

Apply 1–2 times daily

TOBRAMYCIN

Indications and dose

Local treatment of infections (see also notes above)

Child 1–18 years apply twice daily for 6–8 days; in severe infection, apply 4 times daily on the first day, then twice daily for 5–7 days

Tobravise® (Alcon) (PoM)

Eye drops, tobramycin 0.3%, net price 5 mL = £4.74

Excipients include benzododecinium bromide

11.3.2 Antifungals

Fungal infections of the cornea are rare. Orbital mycosis is rarer, and when it occurs it is usually because of direct spread of infection from the paranasal sinuses. Debility or immunosuppression can encourage fungal proliferation. The spread of infection through blood occasionally produces metastatic endophthalmitis.

Many different fungi are capable of producing ocular infection; they can be identified by appropriate laboratory procedures.

Antifungal preparations for the eye are not generally available. Treatment is normally carried out at specialist centres, but requests for information about supplies of preparations not available commercially should be addressed to the Strategic Health Authority (or equivalent in Scotland or Northern Ireland), or to the nearest hospital ophthalmology unit, or to Moorfields Eye Hospital, 162 City Road, London EC1V 2PD (tel. (020) 7253 3411) or www.moorfields.nhs.uk

11.3.3 Antivirals

Herpes simplex infections producing, for example, dendritic corneal ulcers, can be treated with **aciclovir**. Aciclovir eye ointment is used in combination with systemic treatment for ophthalmic zoster (section 5.3.2.1).

For systemic treatment of CMV retinitis, see section 5.3.2.2.

ACICLOVIR (Acyclovir)

Side-effects local irritation and inflammation, superficial punctate keratopathy; *rarely* blepharitis; *very rarely* hypersensitivity reactions including angioedema

Indications and dose

Local treatment of herpes simplex infections

Apply 1 cm ointment 5 times daily (continue for at least 3 days after complete healing)

Herpes simplex skin infections section 13.10.3

Herpes simplex and varicella–zoster infections section 5.3.2.1

Zovirax® (GSK) (PoM)

Eye ointment, aciclovir 3%, net price 4.5 g = £9.34

11.4 Corticosteroids and other anti-inflammatory preparations

11.4.1 Corticosteroids

11.4.2 Other anti-inflammatory preparations

11.4.1 Corticosteroids

Corticosteroids administered locally to the eye or given by mouth are effective for treating anterior segment inflammation in uveitis (section 11.5) and following surgery.

Topical corticosteroids should normally only be used under expert supervision; three main dangers are associated with their use:

- a 'red eye', when the diagnosis is unconfirmed, may be due to herpes simplex virus, and a corticosteroid may aggravate the condition, leading to corneal ulceration, with possible damage to vision and even loss of the eye. Bacterial, fungal, and amoebic infections pose a similar hazard;
- 'steroid glaucoma' may follow the use of corticosteroid eye preparations in susceptible individuals;
- a 'steroid cataract' may follow prolonged use.

Other side-effects of ocular corticosteroids include thinning of the cornea and sclera. Prolonged use in neonates and infants can cause adrenal suppression.

Products combining a corticosteroid with an antimicrobial are used after ocular surgery to reduce inflammation and prevent infection: use of combination products is otherwise rarely justified.

Systemic corticosteroids (section 6.3.2) may be useful for ocular conditions. The risk of producing a 'steroid cataract' increases with the dose and duration of corticosteroid use.

BETAMETHASONE

Cautions see notes above

Side-effects see notes above

Indications and dose**Local treatment of inflammation (short-term)**

Apply eye drops every 1–2 hours until controlled then reduce frequency; eye ointment 2–4 times daily or at night when used with eye drops

Betnesol® (Focus) (PoM)

Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%, net price 10 mL = £2.32

Excipients include benzalkonium chloride, disodium edetate

Eye ointment, betamethasone sodium phosphate 0.1%, net price 3 g = £1.41

Vistamethasone® (Martindale) (PoM)

Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%, net price 5 mL = £1.02; 10 mL = £1.16

Excipients include benzalkonium chloride

With neomycin**Betnesol-N®** (RPH) (PoM) 

Drops (for ear, eye, or nose), see section 12.1.1

DEXAMETHASONE

Cautions see notes above

Side-effects see notes above

Licensed use *Maxidex®* not licensed for use in children under 2 years; *Dropdex®* not licensed for use in children

Indications and dose**Local treatment of inflammation (short-term)**

Apply eye drops 4–6 times daily; severe conditions every 30–60 minutes until controlled then reduce frequency

Maxidex® (Alcon) (PoM)

Eye drops, dexamethasone 0.1%, net price 5 mL = £1.42; 10 mL = £2.80

Excipients include benzalkonium chloride, disodium edetate, polysorbate 80

Single use**Dropdex®** (Moorfields) (PoM)

Eye drops, dexamethasone (as sodium phosphate) 0.1%, net price 20 × 0.4 mL = £9.75

Excipients include disodium edetate

Minims® Dexamethasone (Bausch & Lomb) (PoM)

Eye drops, dexamethasone sodium phosphate 0.1%, net price 20 × 0.5 mL = £10.98

Excipients include disodium edetate

With antibacterials**Maxitrol®** (Alcon) (PoM) 

Eye drops, dexamethasone 0.1%, neomycin sulfate 3500 units/g, polymyxin B sulfate 6000 units/mL, net price 5 mL = £1.68

Excipients include benzalkonium chloride, polysorbate 20

Eye ointment, dexamethasone 0.1%, neomycin sulfate 3500 units/g, polymyxin B sulfate 6000 units/g, net price 3.5 g = £1.44

Excipients include hydroxybenzoates (parabens), wool fat

Sofradex® (Sanofi-Aventis) (PoM) 

Drops (for ear or eye), see section 12.1.1

FLUOROMETHOLONE

Cautions see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 2 years

Indications and dose**Local treatment of inflammation (short-term)**

Apply 2–4 times daily (initially every hour for 24–48 hours then reduce frequency)

FML® (Allergan) (PoM)

Ophthalmic suspension (= eye drops), fluorometholone 0.1%, polyvinyl alcohol (*Liquifilm®*) 1.4%, net price 5 mL = £1.71; 10 mL = £2.95

Excipients include benzalkonium chloride, disodium edetate, polysorbate 80

PREDNISOLONE

Cautions see notes above

Side-effects see notes above

Licensed use *Pred Forte®* not licensed for use in children (age range not specified by manufacturer)

Indications and dose**Local treatment of inflammation (short-term)**

Apply every 1–2 hours until controlled then reduce frequency

Pred Forte® (Allergan) (PoM)

Eye drops, prednisolone acetate 1%, net price 5 mL = £1.52; 10 mL = £3.05

Excipients include benzalkonium chloride, disodium edetate, polysorbate 80

Predsol® (Focus) (PoM)

Drops (for ear or eye), prednisolone sodium phosphate 0.5%, net price 10 mL = £2.00

Excipients include benzalkonium chloride, disodium edetate

Single use**Minims® Prednisolone Sodium Phosphate** (Bausch & Lomb) (PoM)

Eye drops, prednisolone sodium phosphate 0.5%, net price 20 × 0.5 mL = £11.28

Excipients include disodium edetate

11.4.2 Other anti-inflammatory preparations

Eye drops containing antihistamines, such as **antazoline** (with xylometazoline as *Otrivine-Antistin®*), **azelastine**, **epinastine**, **ketotifen**, and **olopatadine**, can be used for allergic conjunctivitis.

Sodium cromoglicate and **nedocromil sodium** eye drops may be useful for vernal keratoconjunctivitis and other allergic forms of conjunctivitis.

Lodoxamide eye drops are used for allergic conjunctival conditions including seasonal allergic conjunctivitis.

Emedastine eye drops are licensed for seasonal allergic conjunctivitis.

ANTAZOLINE SULFATE

Side-effects transient stinging; also reported blurred vision, mydriasis, eye irritation

Indications and dose**Allergic conjunctivitis**

See preparation below

Otrivine-Antistin® (Spectrum Thea)

Eye drops, antazoline sulfate 0.5%, xylometazoline hydrochloride 0.05%, net price 10 mL = £2.35

Excipients include benzalkonium chloride, disodium edetate

Cautions hypertension; hyperthyroidism; diabetes mellitus; angle-closure glaucoma; phaeochromocytoma; cardiovascular disease; urinary retention; **interactions:** Appendix 1 (antihistamines and sympathomimetics)

Dose

Child 12–18 years apply 2–3 times daily (max. duration 7 days)

Note Xylometazoline is a sympathomimetic; absorption of antazoline and xylometazoline may result in systemic side-effects and the possibility of interaction with other drugs

AZELASTINE HYDROCHLORIDE

Side-effects mild transient irritation; bitter taste reported

Indications and dose

Allergic conjunctivitis, seasonal allergic conjunctivitis

Child 4–18 years apply twice daily, increased if necessary to 4 times daily

Perennial conjunctivitis

Child 12–18 years apply twice daily, increased if necessary to 4 times daily; max. duration of treatment 6 weeks

Optilast® (Meda) (PoM)

Eye drops, azelastine hydrochloride 0.05%, net price 8 mL = £6.40

Excipients include benzalkonium chloride, disodium edetate

EMEDASTINE

Side-effects transient burning or stinging; blurred vision, local oedema, keratitis, irritation, dry eye, lacrimation, corneal infiltrates (discontinue) and staining; photophobia; headache, and rhinitis occasionally reported

Indications and dose

Seasonal allergic conjunctivitis

Child 3–18 years apply twice daily

Emadine® (Alcon) (PoM)

Eye drops, emedastine 0.05% (as difumate), net price 5 mL = £7.31

Excipients include benzalkonium chloride

EPINASTINE HYDROCHLORIDE

Side-effects burning; *less commonly* taste disturbance, headache, conjunctival hyperaemia, dry eye, eye pruritus, visual disturbance, increased lacrimation, eye pain, nasal irritation, rhinitis

Indications and dose

Seasonal allergic conjunctivitis

Child 12–18 years apply twice daily; max. duration of treatment 8 weeks

Relestat® (Allergan) (PoM)

Eye drops, epinastine hydrochloride 500 micrograms/mL, net price 5 mL = £9.90

Excipients include benzalkonium chloride, disodium edetate

KETOTIFEN

Side-effects transient burning or stinging, punctate corneal epithelial erosion; *less commonly* dry eye, subconjunctival haemorrhage, photophobia; headache, drowsiness, skin reactions, and dry mouth also reported

Indications and dose

Seasonal allergic conjunctivitis

Child 3–18 years apply twice daily

Zaditen® (Spectrum Thea) (PoM)

Eye drops, ketotifen (as fumarate) 250 micrograms/mL, net price 5 mL = £7.80

Excipients include benzalkonium chloride

LODOXAMIDE

Side-effects burning, stinging, itching, blurred vision, tear production disturbance, and ocular discomfort; *less commonly*, flushing, nasal dryness, dizziness, drowsiness, headache, blepharitis, and keratitis

Indications and dose

Allergic conjunctivitis

Child 4–18 years apply 4 times daily

Note Improvement of symptoms may sometimes require treatment for up to 4 weeks

Alomide® (Alcon) (PoM)

Ophthalmic solution (= eye drops), lodoxamide (as trometamol) 0.1%, net price 10 mL = £5.21

Excipients include benzalkonium chloride, disodium edetate

Note Lodoxamide 0.1% eye drops can be sold to the public for treatment of allergic conjunctivitis in children over 4 years

NEDOCROMIL SODIUM

Side-effects transient burning and stinging; distinctive taste reported

Indications and dose

Seasonal and perennial allergic conjunctivitis

Child 6–18 years apply twice daily increased if necessary to 4 times daily; max. 12 weeks treatment for seasonal allergic conjunctivitis

Vernal keratoconjunctivitis

Child 6–18 years apply 4 times daily

Rapitil® (Sanofi-Aventis) (PoM)

Eye drops, nedocromil sodium 2%, net price 5 mL = £2.86

Excipients include benzalkonium chloride, disodium edetate

OLOPATADINE

Side-effects local irritation; *less commonly* keratitis, dry eye, local oedema, photophobia; headache, asthenia, dizziness; dry nose also reported

Indications and dose

Seasonal allergic conjunctivitis

Child 3–18 years apply twice daily; max. duration of treatment 4 months

Opatanol® (Alcon) (PoM)

Eye drops, olopatadine (as hydrochloride) 1 mg/mL, net price 5 mL = £4.68

Excipients include benzalkonium chloride

SODIUM CROMOGLICATE

(Sodium cromoglycate)

Side-effects transient burning and stinging**Indications and dose****Allergic conjunctivitis, vernal keratoconjunctivitis**

Apply eye drops 4 times daily

Sodium Cromoglicate (Non-proprietary) (PoM)**Eye drops**, sodium cromoglycate 2%, net price

13.5 mL = £1.67

Brands include Hay-Crom® Aqueous, Opticrom® Aqueous, Vividrin®**Note** Sodium cromoglycate 2% eye drops can be sold to the public (in max. pack size of 10 mL) for treatment of acute seasonal and perennial allergic conjunctivitis**Single use****Catacrom®** (Moorfields)**Eye drops**, sodium cromoglycate 2%, net price 30 × 0.3 mL = £8.99

11.5 Mydriatics and cycloplegics

Antimuscarinics dilate the pupil and paralyse the ciliary muscle; they vary in potency and duration of action.

Short-acting, relatively weak mydriatics, such as **tropicamide** 0.5% (action lasts for 4–6 hours), facilitate the examination of the fundus of the eye. **Cyclopentolate** 1% (action up to 24 hours) or **atropine** (action up to 7 days) are preferable for producing cycloplegia for refraction in young children; tropicamide may be preferred in neonates. **Phenylephrine** 2.5% is used for mydriasis in diagnostic or therapeutic procedures; mydriasis occurs within 60–90 minutes and lasts up to 5–7 hours.

Mydriatics and cycloplegics are used in the treatment of anterior uveitis, usually as an adjunct to corticosteroids (section 11.4.1). Atropine is used in anterior uveitis mainly to prevent posterior synechiae and to relieve ciliary spasm; cyclopentolate or **homatropine** (action up to 3 days) can also be used and may be preferred because they have a shorter duration of action.

Cautions and contra-indications Darkly pigmented irides are more resistant to pupillary dilatation and caution should be exercised to avoid overdosage. Mydriasis can precipitate acute angle-closure glaucoma in the very few children who are predisposed to the condition because of a shallow anterior chamber. Atropine, cyclopentolate, and homatropine should be used with caution in children under 3 months owing to the possible association between cycloplegia and the development of amblyopia; also, neonates are at increased risk of systemic toxicity.

Skilled tasks Children may not be able to undertake skilled tasks until vision clears after mydriasis.

Side-effects Ocular side-effects of mydriatics and cycloplegics include transient stinging and raised intra-ocular pressure; on prolonged administration, local irritation, hyperaemia, oedema, and conjunctivitis can occur. Contact dermatitis can occur with the antimuscarinic mydriatic drugs, especially atropine.

Toxic systemic reactions to atropine and cyclopentolate can occur in neonates and children; see section 1.2 for systemic side-effects of antimuscarinic drugs.

Antimuscarinics**ATROPINE SULFATE****Cautions** see notes above**Side-effects** see notes above**Licensed use** not licensed for use in children for uveitis**Indications and dose****Cycloplegia****Child 3 months–18 years** apply drops or ointment twice daily for 3 days before procedure**Anterior uveitis****Child 2–18 years** 1 drop up to 4 times daily**Atropine** (Non-proprietary) (PoM)**Eye drops**, atropine sulfate 0.5%, net price 10 mL = £20.91; 1%, 10 mL = £13.25**Single use****Minims® Atropine Sulphate** (Bausch & Lomb) (PoM)**Eye drops**, atropine sulfate 1%, net price 20 × 0.5 mL = £14.46**CYCLOPENTOLATE HYDROCHLORIDE****Cautions** see notes above**Side-effects** see notes above**Indications and dose**

See notes above

Cycloplegia**Child 3 months–12 years** 1 drop of 1% eye drops 30–60 minutes before examination**Child 12–18 years** 1 drop of 0.5% eye drops 30–60 minutes before examination**Uveitis****Child 3 months–18 years** 1 drop of 0.5% eye drops (1% for deeply pigmented eyes) 2–4 times daily**Mydrilate®** (Intrapharm) (PoM)**Eye drops**, cyclopentolate hydrochloride 0.5%, net price 5 mL = £6.73; 1%, 5 mL = £6.73**Excipients** include benzalkonium chloride**Single use****Minims® Cyclopentolate Hydrochloride** (Bausch & Lomb) (PoM)**Eye drops**, cyclopentolate hydrochloride 0.5% and 1%, net price 20 × 0.5 mL (both) = £9.64**HOMATROPINE HYDROBROMIDE****Cautions** see notes above**Side-effects** see notes above**Licensed use** not licensed for use in children under 3 months**Indications and dose**

See notes above

Child 3 months–2 years (0.5% only) 1 drop daily or on alternate days adjusted according to response**Child 2–18 years** 1 drop twice daily adjusted according to response

Homatropine (Non-proprietary) (PoM)

Eye drops, homatropine 0.125% and 0.5%, 10 mL, available as a manufactured special from Moorfields Eye Hospital, see also 'special-order' manufacturers or specialist importing companies, p. 840

TROPICAMIDE

Cautions see notes above

Side-effects see notes above

Indications and dose

See notes above

Funduscopy

Neonate and child apply 0.5% eye drops 20 minutes before examination

Mydracil® (Alcon) (PoM)

Eye drops, tropicamide 0.5%, net price 5 mL = £1.29; 1%, 5 mL = £1.60

Excipients include benzalkonium chloride, disodium edetate

Single use**Minims® Tropicamide** (Bausch & Lomb) (PoM)

Eye drops, tropicamide 0.5% and 1%, net price 20 × 0.5 mL (both) = £10.00

Sympathomimetics**PHENYLEPHRINE HYDROCHLORIDE**

Cautions see notes above; also corneal epithelial damage; ocular hyperaemia; susceptibility to angle-closure glaucoma; diabetes (avoid in long-standing diabetes); asthma; **interactions**: Appendix 1 (sympathomimetics)

Contra-indications 10% drops in neonates and children; cardiovascular disease; hypertension; aneurysms; thyrotoxicosis

Pregnancy use only if potential benefit outweighs risk

Breast-feeding use only if potential benefit outweighs risk—no information available

Side-effects see notes above; also blurred vision, photophobia; systemic effects include palpitations, tachycardia, extrasystoles, arrhythmias, hypertension; also reported coronary artery spasm, myocardial infarction (usually after use of 10% strength in patients with pre-existing cardiovascular disease)

Indications and dose**Mydriasis**

Apply 1 drop before procedure; see also notes above

Note A drop of proxymetacaine topical anaesthetic may be applied to the eye a few minutes before using phenylephrine to prevent stinging

Single use**Minims® Phenylephrine Hydrochloride** (Bausch & Lomb)

Eye drops, phenylephrine hydrochloride 2.5%, net price 20 × 0.5 mL = £10.93

Excipients include disodium edetate, sodium metabisulfite

11.6 Treatment of glaucoma

Glaucoma describes a group of disorders characterised by a loss of visual field associated with cupping of the optic disc and optic nerve damage and is generally associated with raised intra-ocular pressure.

Glaucoma is rare in children and should always be managed by a specialist. *Primary congenital glaucoma* is the most common form of glaucoma in children, followed by *secondary glaucomas*, such as following hereditary anterior segment malformations; *juvenile open-angle glaucoma* is less common and usually occurs in older children. *Primary angle closure glaucoma* (acute closed-angle glaucoma) is very rare in children; it is a medical emergency that requires urgent reduction of intra-ocular pressure, see below. Outflow of aqueous humour from the eye is obstructed by bowing of the iris against the trabecular meshwork.

Treatment of glaucoma is determined by the pathophysiology and usually involves controlling raised intra-ocular pressure with surgery. Drug therapy is generally supportive, and can be used temporarily, pre- or post-operatively, or both, to reduce intra-ocular pressure. In secondary glaucomas, drug therapy is often used first-line, and long-term treatment may be required. Drugs that reduce intra-ocular pressure by different mechanisms are available for managing glaucoma. A topical beta-blocker or a prostaglandin analogue can be used. It may be necessary to combine these drugs or add others, such as carbonic anhydrase inhibitors, or miotics to control intra-ocular pressure.

Acetazolamide by intravenous injection can be used for the emergency management of raised intra-ocular pressure. Rarely, **mannitol** can be given by slow intravenous infusion to reduce intra-ocular pressure (see section 2.2.5).

Beta-blockers

Topical application of a beta-blocker to the eye reduces intra-ocular pressure effectively in primary and secondary glaucomas, probably by reducing the rate of production of aqueous humour.

Cautions, contra-indications, and side-effects

Systemic absorption can follow topical application to the eye; therefore, eye drops containing a beta-blocker are contra-indicated in bradycardia, heart block, or uncontrolled heart failure. **Important:** for a warning to avoid in asthma, see below. Cough, rather than wheeze, may occur in children using topical beta-blockers. Consider also other cautions, contra-indications, and side-effects of beta-blockers (p. 87). Beta-blocker eye drops should be used with caution in children with corneal diseases. Local side-effects of eye drops include ocular stinging, burning, pain, itching, erythema, dry eyes and allergic reactions including anaphylaxis and blepharoconjunctivitis; occasionally corneal disorders have been reported.

Important Beta-blockers, even those with apparent cardioselectivity, should not be used in patients with asthma or a history of bronchospasm, unless no alternative treatment is available. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.

Interactions Since systemic absorption may follow topical application the possibility of interactions, in particular with drugs such as verapamil, should be borne in mind. See also Appendix 1 (beta-blockers).

BETAXOLOL

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children

Indications and dose

See notes above

Apply twice daily

Betaxolol (Non-proprietary) (PoM)**Eye drops**, solution, betaxolol (as hydrochloride) 0.5%, net price 5 mL = £1.90**Excipients** may include benzalkonium chloride, disodium edetate**Betoptol**® (Alcon) (PoM)**Ophthalmic solution** (= eye drops), betaxolol (as hydrochloride) 0.5%, net price 5 mL = £1.90**Excipients** include benzalkonium chloride, disodium edetate**Ophthalmic suspension** (= eye drops), betaxolol (as hydrochloride) 0.25%, net price 5 mL = £2.66**Excipients** include benzalkonium chloride, disodium edetate**Unit dose eye drop suspension**, betaxolol (as hydrochloride) 0.25%, net price 50 × 0.25 mL = £13.77**CARTEOLOL HYDROCHLORIDE****Cautions** see notes above**Contra-indications** see notes above**Side-effects** see notes above**Licensed use** not licensed for use in children**Indications and dose**

See notes above

Apply twice daily

Teoptic® (Spectrum Thea) (PoM)**Eye drops**, carteolol hydrochloride 1%, net price 5 mL = £7.60; 2%, 5 mL = £8.40**Excipients** include benzalkonium chloride**LEVOBUNOLOL HYDROCHLORIDE****Cautions** see notes above**Contra-indications** see notes above**Side-effects** see notes above; anterior uveitis occasionally reported**Licensed use** not licensed for use in children**Indications and dose**

See notes above

Apply once or twice daily

Levobunolol (Non-proprietary) (PoM)**Eye drops**, levobunolol hydrochloride 0.5%, net price 5 mL = £1.85**Excipients** may include benzalkonium chloride, disodium edetate, sodium metabisulfite**Betagan**® (Allergan) (PoM)**Eye drops**, levobunolol hydrochloride 0.5%, polyvinyl alcohol (*Liquifilm*®) 1.4%, net price 5-mL = £1.85**Excipients** include benzalkonium chloride, disodium edetate, sodium metabisulfite**Unit dose eye drops**, levobunolol hydrochloride 0.5%, polyvinyl alcohol (*Liquifilm*®) 1.4%, net price 30 × 0.4 mL = £9.98**Excipients** include disodium edetate**TIMOLOL****Cautions** see notes above**Contra-indications** see notes above**Side-effects** see notes above**Licensed use** not licensed for use in children**Indications and dose**

See notes above

Apply twice daily; long-acting preparations, see under preparations below

Timolol (Non-proprietary) (PoM)**Eye drops**, timolol (as maleate) 0.25%, net price 5 mL = £1.30; 0.5%, 5 mL = £1.22**Timoptol**® (MSD) (PoM)**Eye drops**, in *Ocumeter*® metered-dose unit, timolol (as maleate) 0.25%, net price 5 mL = £3.12; 0.5%, 5 mL = £3.12**Excipients** include benzalkonium chloride**Unit dose eye drops**, timolol (as maleate) 0.25%, net price 30 × 0.2 mL = £8.45; 0.5%, 30 × 0.2 mL = £9.65**Once-daily preparations****Timoptol**®-LA (MSD) (PoM)**Ophthalmic gel-forming solution** (= eye drops), timolol (as maleate) 0.25%, net price 2.5 mL = £3.12; 0.5%, 2.5 mL = £3.12**Excipients** include benzododecinium bromide**Dose**

Apply eye drops once daily

Tiopex® (Spectrum Thea) (PoM)**Unit dose eye gel** (= eye drops), timolol (as maleate) 0.1%, net price 30 × 0.4 g = £7.49**Dose**

Apply once daily in the morning

Note The *Scottish Medicines Consortium* (p. 3) has advised (February 2014) that timolol gel eye drops (*Tiopex*®) are accepted for restricted use within NHS Scotland for the reduction of elevated intraocular pressure in patients with ocular hypertension or chronic open angle glaucoma who have proven sensitivity to preservatives.**With dorzolamide**

See under Dorzolamide

Prostaglandin analoguesThe prostaglandin analogues **latanoprost**, and **travoprost**, and the synthetic prostamide, **bimatoprost**, increase uveoscleral outflow and subsequently reduce intra-ocular pressure. They are used to reduce intra-ocular pressure. Only latanoprost (*Xalatan*®) and certain non-proprietary preparations of latanoprost is licensed for use in children. Children receiving prostaglandin analogues should be managed by a specialist.**LATANOPROST****Cautions** monitor for changes to eye coloration—see Counselling below; peri-operative period of cataract surgery; history of herpetic keratitis; aphakia, pseudophakia with torn posterior lens capsule or anterior chamber lenses; risk factors for cystoid macular oedema, iritis, or uveitis; history of significant ocular viral infections; asthma; preterm neonates less than 36 weeks gestational age—no information available; children less than 1 year—limited information available**Contra-indications** active herpes simplex keratitis and history of recurrent herpetic keratitis associated with prostaglandin analogues**Pregnancy** manufacturer advises avoid

Breast-feeding may be present in milk—manufacturer advises avoid

Side-effects eye pain, transient punctate epithelial erosions, blepharitis, increased iris pigmentation, conjunctival hyperaemia, eye irritation, eyelash and vellus hair changes; *less commonly* eyelid oedema, dry eye, keratitis, blurred vision, conjunctivitis, skin rash; *rarely* iritis, uveitis, macular oedema, corneal oedema and erosions, periorbital oedema, misdirected eyelashes, distichiasis, photophobia; *very rarely* chest pain, periorbital and lid changes resulting in deepening of the eyelid sulcus, localised skin reaction on the eyelids, darkening of the palpebral skin of the eyelids; *also reported* palpitations, asthma, exacerbation of asthma, dyspnoea, headache, dizziness, pyrexia, myalgia, arthralgia, herpetic keratitis, iris cyst, nasopharyngitis

Indications and dose

Reduction of intra-ocular pressure in raised intra-ocular pressure and glaucoma

Apply once daily, preferably in the evening

Counselling Before initiating treatment, children and their carers should be warned of a possible change in eye colour as an increase in the brown pigment in the iris can occur, which may be permanent; particular care is required in those with mixed coloured irides and those receiving treatment to one eye only. Changes in eyelashes and vellus hair can also occur, and children and their carers should also be advised to avoid repeated contact of the eye drop solution with skin as this can lead to hair growth or skin pigmentation.

Latanoprost (Non-proprietary) (POM)

Eye drops, latanoprost 50 micrograms/mL, net price 2.5 mL = £1.97. Counselling, see Counselling, p. 533

Excipients may include benzalkonium chloride

Xalatan® (Pfizer) (POM)

Eye drops, latanoprost 50 micrograms/mL, net price 2.5 mL = £12.48. Counselling, see Counselling, p. 533

Excipients include benzalkonium chloride

Sympathomimetics

Apraclonidine (section 11.8.2) is an α_2 -adrenoceptor agonist that lowers intra-ocular pressure by reducing aqueous humour formation. Eye drops containing apraclonidine 0.5% are used for a short period to delay laser treatment or surgery for glaucoma in patients not adequately controlled by another drug; eye drops containing 1% are used for control of intra-ocular pressure after anterior segment laser surgery.

Brimonidine, an α_2 -adrenoceptor agonist, is thought to lower intra-ocular pressure by reducing aqueous humour formation and increasing uveoscleral outflow; it is contra-indicated in neonates and children under 2 years (risk of severe systemic side-effects), and should be used with caution in children 2–12 years (increased risk of drowsiness).

Carbonic anhydrase inhibitors and systemic drugs

The **carbonic anhydrase inhibitors**, acetazolamide, brinzolamide, and dorzolamide, reduce intra-ocular pressure by reducing aqueous humour production. Systemic use of acetazolamide also produces weak diuresis.

Acetazolamide is given by mouth or, rarely in children, by intravenous injection (intramuscular injections are painful because of the alkaline pH of the solution). It is

used as an adjunct to other treatment for reducing intra-ocular pressure. Acetazolamide is a sulfonamide derivative; blood disorders, rashes, and other sulfonamide-related side-effects occur occasionally—children and their carers should be told to report any unusual skin rash. It is not generally recommended for long-term use; if electrolyte disturbances and metabolic acidosis occur, they can be corrected by administering potassium bicarbonate (as effervescent potassium tablets, section 9.2.1.3).

Dorzolamide and **brinzolamide** are topical carbonic anhydrase inhibitors. They are unlicensed in children but are used in those resistant to beta-blockers or those in whom beta-blockers are contra-indicated. They are used alone or as an adjunct to a topical beta-blocker. Brinzolamide can also be used as an adjunct to a prostaglandin analogue. Systemic absorption can rarely cause sulfonamide-like side-effects and may require discontinuation if severe.

Metabolic acidosis can occur in children using topical carbonic anhydrase inhibitors; symptoms may include poor feeding and lack of weight gain.

ACETAZOLAMIDE

Cautions not generally recommended for prolonged use, but if given, monitor blood count and plasma electrolyte concentrations; pulmonary obstruction and impaired alveolar ventilation (risk of acidosis); diabetes mellitus; renal calculi; avoid extravasation at injection site (risk of necrosis); **interactions:** Appendix 1 (diuretics)

Contra-indications hypokalaemia, hyponatraemia, hyperchloraemic acidosis; adrenocortical insufficiency; long-term administration in chronic angle-closure glaucoma; sulfonamide hypersensitivity

Hepatic impairment manufacturer advises avoid

Renal impairment avoid; metabolic acidosis

Pregnancy manufacturer advises avoid, especially in first trimester (toxicity in *animal studies*)

Breast-feeding amount too small to be harmful

Side-effects see notes above; also nausea, vomiting, diarrhoea, taste disturbance, loss of appetite, paraesthesia, flushing, headache, dizziness, fatigue, irritability, excitement, ataxia, depression, thirst, polyuria; *less commonly* melaena, drowsiness, confusion, hearing disturbances, fever, glycosuria, metabolic acidosis and electrolyte disturbances on long-term therapy, haematuria, crystalluria, renal and ureteral colic, renal lesions or calculi, renal failure, blood disorders, bone marrow suppression, rash (including Stevens-Johnson syndrome and toxic epidermal necrosis); *rarely* fulminant hepatic necrosis, hepatitis, cholestatic jaundice, flaccid paralysis, convulsions, photosensitivity; *also reported* transient myopia

Licensed use not licensed for use in children for treatment of glaucoma

Indications and dose

Reduction of intra-ocular pressure in primary and secondary glaucoma

• By mouth or by intravenous injection

Child 1 month–12 years 5 mg/kg 2–4 times daily, adjusted according to response, max. 750 mg daily

Child 12–18 years 250 mg 2–4 times daily

Epilepsy

● By mouth or slow intravenous injection

Neonate initially 2.5 mg/kg 2–3 times daily, followed by 5–7 mg/kg 2–3 times daily (maintenance dose)

Child 1 month–12 years initially 2.5 mg/kg 2–3 times daily, followed by 5–7 mg/kg 2–3 times daily, max. 750 mg daily (maintenance dose)

Child 12–18 years 250 mg 2–4 times daily

Raised intracranial pressure

● By mouth or slow intravenous injection

Child 1 month–12 years initially 8 mg/kg 3 times daily, increased as necessary to max. 100 mg/kg daily

Diamox® (AMCO) (PoM)

Tablets, acetazolamide 250 mg, net price 112-tab pack = £15.22. Label: 3

Injection, powder for reconstitution, acetazolamide (as sodium salt), net price 500-mg vial = £14.76

■ **Modified release****Diamox® SR (AMCO) (PoM)**

Capsules, m/r, orange, enclosing orange f/c pellets, acetazolamide 250 mg, net price 30-cap pack = £16.66. Label: 3, 25

Dose

Child 12–18 years glaucoma, 1–2 capsules daily

BRINZOLAMIDE

Cautions systemic absorption follows topical application; renal tubular immaturity or abnormality—risk of metabolic acidosis; **interactions:** Appendix 1 (brinzolamide)

Contra-indications hyperchloraemic acidosis; sulfonamide hypersensitivity

Hepatic impairment manufacturer advises avoid

Renal impairment see Cautions above; also avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy avoid—toxicity in animal studies

Breast-feeding use only if benefit outweighs risk

Side-effects see notes above; also taste disturbances, dry mouth, headache, ocular disturbances (including corneal erosion, corneal oedema, photophobia, and reduced visual acuity); *less commonly* nausea, vomiting, diarrhoea, dyspepsia, oesophagitis, flatulence, oral hypoesthesia and paraesthesia, chest pain, bradycardia, palpitation, dyspnoea, cough, upper respiratory tract congestion, pharyngitis, depression, sleep disturbances, nervousness, malaise, drowsiness, amnesia, dizziness, paraesthesia, sinusitis, decreased libido, erectile dysfunction, renal pain, epistaxis, nasal dryness, throat irritation, tinnitus, alopecia; *also reported* arrhythmia, tachycardia, hypertension, peripheral oedema, asthma, tremor, vertigo, pollakiuria, rhinitis, dermatitis, erythema

Licensed use not licensed for use in children

Indications and dose

Reduction of intra-ocular pressure in primary and secondary glaucoma either as adjunct to beta-blockers or prostaglandin analogues or used alone if unresponsive to beta-blockers or if beta-blockers contra-indicated

Apply twice daily, increased to max. 3 times daily if necessary

Azopt® (Alcon) (PoM)

Eye drops, brinzolamide 10 mg/mL, net price 5 mL = £6.92

Excipients include benzalkonium chloride, disodium edetate

DORZOLAMIDE

Cautions systemic absorption follows topical application; history of renal calculi; neonates and infants with immature renal tubules—risk of metabolic acidosis; chronic corneal defects, low endothelial cell count, history of intra-ocular surgery; **interactions:** Appendix 1 (dorzolamide)

Contra-indications hyperchloraemic acidosis

Hepatic impairment manufacturer advises caution—no information available

Renal impairment see Cautions above; also avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid—toxicity in animal studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above; also nausea, bitter taste, headache, asthenia, ocular irritation, blurred vision, lacrimation, conjunctivitis, superficial punctate keratitis, eyelid inflammation; *less commonly* iridocyclitis; *rarely* dry mouth, dizziness, paraesthesia, urolithiasis, eyelid crusting, transient myopia, corneal oedema, epistaxis, throat irritation, contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis; *also reported* metabolic acidosis

Licensed use not licensed for use in children

Indications and dose

Raised intra-ocular pressure in primary and secondary glaucoma either as adjunct to beta-blocker or used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated

Used alone, apply 3 times daily; with topical beta-blocker, apply twice daily

Dorzolamide (Non-proprietary) (PoM)

Eye drops, dorzolamide (as hydrochloride) 2%, net price 5 mL = £1.99

Excipients may include benzalkonium chloride

Brands include Dorzant®

Trusopt® (MSD) (PoM)

Ophthalmic solution (= eye drops), in Ocumeter® Plus metered-dose unit, dorzolamide (as hydrochloride) 2%, net price 5 mL = £6.33

Excipients include benzalkonium chloride

Unit dose eye drops, dorzolamide (as hydrochloride) 2%, net price 60 × 0.2 mL = £24.18

■ **With timolol**

For prescribing information on timolol, see section 11.6, Beta-blockers

Dorzolamide with Timolol (Non-proprietary) (PoM)

Eye drops, dorzolamide (as hydrochloride) 2%, timolol (as maleate) 0.5%, net price 5 mL = £2.90

Excipients may include benzalkonium chloride

Cosopt® (MSD) (PoM)

Ophthalmic solution (= eye drops), in Ocumeter® Plus metered-dose unit, dorzolamide (as hydrochloride) 2%, timolol (as maleate) 0.5%, net price 5 mL = £10.05

Excipients include benzalkonium chloride

Unit dose eye drops, dorzolamide (as hydrochloride) 2%, timolol (as maleate) 0.5%, net price 60 × 0.2 mL = £28.59

Dose

Raised intra-ocular pressure in open-angle glaucoma, or pseudoexfoliative glaucoma when beta-blockers alone not adequate

Apply twice daily

Miotics

Miotics act by opening up the inefficient drainage channels in the trabecular meshwork. **Pilocarpine** is a miotic used pre- and postoperatively in goniotomy and trabeculotomy; it is used occasionally for aphakic glaucoma.

Cautions A darkly pigmented iris may require a higher concentration of the miotic or more frequent administration and care should be taken to avoid over-dosage. Retinal detachment has occurred in susceptible individuals and those with retinal disease; therefore fundus examination is advised before starting treatment with a miotic. Care is also required in conjunctival or corneal damage. Intra-ocular pressure and visual fields should be monitored in those with chronic simple glaucoma and those receiving long-term treatment with a miotic. Miotics should be used with caution in patients with peptic ulceration, gastro-intestinal spasm, cardiac disease, hypertension, hypotension, asthma, epilepsy, hyperthyroidism, and urinary-tract obstruction.

Counselling Blurred vision may affect performance of skilled tasks (e.g. cycling or driving) particularly at night or in reduced lighting

Contra-indications Miotics are contra-indicated in conditions where pupillary constriction is undesirable such as acute iritis, anterior uveitis and some forms of secondary glaucoma. They should be avoided in acute inflammatory disease of the anterior segment.

Pregnancy Miotics should be avoided unless the potential benefit outweighs the risk—limited information available.

Breast-feeding Miotics should be avoided unless the potential benefit outweighs the risk—no information available.

Side-effects Ciliary spasm leads to headache and browache which may be more severe in the initial 2–4 weeks of treatment. Ocular side-effects include burning, itching, smarting, blurred vision, conjunctival vascular congestion, myopia, lens changes with chronic use, vitreous haemorrhage, and pupillary block. Systemic side-effects are rare following application to the eye.

PILOCARPINE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children

Indications and dose

See also notes above

Raised intra-ocular pressure

- **Child 1 month–2 years** 1 drop of 0.5% or 1% solution 3 times daily
- **Child 2–18 years** 1 drop 4 times daily

Pre- and postoperatively in goniotomy and trabeculotomy

Child 1 month–18 years apply 1% or 2% solution once daily

Pilocarpine Hydrochloride (Non-proprietary) (PoM)

Eye drops, pilocarpine hydrochloride 1%, net price 10 mL = £2.32; 2%, 10 mL = £2.74; 4%, 10 mL = £3.46

Excipients may include benzalkonium chloride

Single use

Minims® Pilocarpine Nitrate (Bausch & Lomb) (PoM)

Eye drops, pilocarpine nitrate 2%, net price 20 × 0.5 mL = £11.48

11.7 Local anaesthetics

Oxybuprocaine and **tetracaine** are widely used topical local anaesthetics. **Proxymetacaine** causes less initial stinging and is particularly useful for children. **Oxybuprocaine** or a combined preparation of lidocaine and fluorescein is used for tonometry. **Tetracaine** produces more profound anaesthesia and is suitable for use before minor surgical procedures, such as the removal of corneal sutures. It has a temporary disruptive effect on the corneal epithelium. **Lidocaine**, with or without adrenaline (epinephrine), is injected into the eyelids for minor surgery, see section 15.2, p. 654. Local anaesthetics should never be used for the management of ocular symptoms.

Cautions Local anaesthetic eye drops should be avoided in preterm neonates because of the immaturity of the metabolising enzyme system.

LIDOCAINE HYDROCHLORIDE (Lignocaine hydrochloride)

Contra-indications avoid in preterm neonates

Indications and dose

Local anaesthetic

Use as required

Minims® Lidocaine and Fluorescein (Bausch & Lomb) (PoM)

Eye drops, lidocaine hydrochloride 4%, fluorescein sodium 0.25%, net price 20 × 0.5 mL = £11.24

OXYBUPROCAINE HYDROCHLORIDE (Benoxinate hydrochloride)

Contra-indications avoid in preterm neonates

Indications and dose

Local anaesthetic

Use as required

Minims® Oxybuprocaine Hydrochloride (Bausch & Lomb) (PoM)

Eye drops, oxybuprocaine hydrochloride 0.4%, net price 20 × 0.5 mL = £9.72

PROXYMETACAINE HYDROCHLORIDE

Contra-indications avoid in preterm neonates

Indications and dose

Local anaesthetic

Use as required

Minims® Proxymetacaine (Bausch & Lomb) (PoM)

Eye drops, proxymetacaine hydrochloride 0.5%, net price 20 × 0.5 mL = £11.05

▲ **With fluorescein****Minims® Proxymetacaine and Fluorescein** (Bausch & Lomb) (PoM)

Eye drops, proxymetacaine hydrochloride 0.5%, fluorescein sodium 0.25%, net price 20 × 0.5 mL = £12.12

TETRACAINE HYDROCHLORIDE
(Amethocaine hydrochloride)

Contra-indications avoid in preterm neonates

Indications and dose**Local anaesthetic**

Use as required

Minims® Tetracaine Hydrochloride (Bausch & Lomb) (PoM)

Eye drops, tetracaine hydrochloride 0.5% and 1%, net price 20 × 0.5 mL (both) = £9.73

11.8 Miscellaneous ophthalmic preparations**11.8.1 Tear deficiency, ocular lubricants, and astringents****11.8.2 Ocular diagnostic and peri-operative preparations**

Certain eye drops, e.g. amphotericin, ceftazidime, cefuroxime, colistimethate sodium, desferrioxamine, dexamethasone, gentamicin, and vancomycin, can be prepared aseptically in a specialist manufacturing unit from material supplied for injection.

Preparations may also be available from Moorfields Eye Hospital as manufactured specials, see also 'special-order' manufacturers or specialist importing companies, p. 840.

11.8.1 Tear deficiency, ocular lubricants, and astringents

Chronic soreness of the eyes associated with reduced or abnormal tear secretion often responds to tear replacement therapy. The severity of the condition and the child's preference will often guide the choice of preparation.

Hypromellose is the traditional choice of treatment for tear deficiency. It may need to be instilled frequently (e.g. hourly) for adequate relief. Ocular surface mucin is often abnormal in tear deficiency and the combination of hypromellose with a mucolytic such as **acetylcysteine** can be helpful.

The ability of **carbomers** to cling to the eye surface may help reduce frequency of application to 4 times daily.

Polyvinyl alcohol increases the persistence of the tear film and is useful when the ocular surface mucin is reduced.

Sodium hyaluronate eye drops are also used in the management of tear deficiency.

Sodium chloride 0.9% drops are sometimes useful in tear deficiency, and can be used as 'comfort drops' by

contact lens wearers, and to facilitate lens removal. Special presentations of sodium chloride 0.9% and other irrigation solutions are used routinely for intra-ocular surgery and in first-aid for removal of harmful substances.

Eye ointments containing a **paraffin** can be used to lubricate the eye surface, especially in cases of recurrent corneal epithelial erosion. They may cause temporary visual disturbance and are best suited for application before sleep. Ointments should not be used during contact lens wear.

ACETYL CYSTEINE**Indications and dose****Tear deficiency, impaired or abnormal mucus production**

Apply 3–4 times daily

Ilube® (Moorfields) (PoM)

Eye drops, acetylcysteine 5%, hypromellose 0.35%, net price 10 mL = £10.09

Excipients include benzalkonium chloride, disodium edetate

CARBOMERS
(Polyacrylic acid)

Synthetic high molecular weight polymers of acrylic acid cross-linked with either allyl ethers of sucrose or allyl ethers of pentaerythritol

Licensed use some preparations not licensed for use in children

Indications and dose**Dry eyes including keratoconjunctivitis sicca, unstable tear film**

Apply 3–4 times daily or as required

Artelac® Nighttime Gel (Bausch & Lomb)

Gel (= eye drops), carbomer 2 mg, net price 10 g = £2.96

GelTears® (Bausch & Lomb)

Gel (= eye drops), carbomer 980 (polyacrylic acid) 0.2%, net price 10 g = £2.80

Excipients include benzalkonium chloride

Liquivisc® (Spectrum Thea)

Gel (= eye drops), carbomer 974P (polyacrylic acid) 0.25%, net price 10 g = £4.50

Excipients include benzalkonium chloride

Lumecare® Carbomer Gel (Medicom)

Gel (= eye drops), carbomer 980 (polyacrylic acid) 0.2%, net price 10 g = £2.10

Excipients include cetrimide

Viscotears® (Alcon)

Liquid gel (= eye drops), carbomer 980 (polyacrylic acid) 0.2%, net price 10 g = £1.59

Excipients include cetrimide

▲ **Single use****Viscotears®** (Alcon)

Liquid gel (= eye drops), carbomer 980 (polyacrylic acid) 0.2%, net price 30 × 0.6-mL = £5.42

CARMELLOSE SODIUM**Indications and dose****Dry eye conditions**

Apply as required

Carmellose (Non-proprietary)

Eye drops, carmellose sodium 0.5%, net price 10 mL = £7.49

Carimize® (Aspire)

Eye drops, carmellose sodium 0.5%, net price 10 mL = £7.49

Optive® (Allergan)

Eye drops, carmellose sodium 0.5%, glycerol, net price 10 mL = £7.49

▲ **Single use****Carmellose** (Non-proprietary)

Eye drops, carmellose sodium 0.5%, net price 30 × 0.4 mL = £5.75

Carimize® (Aspire)

Eye drops, carmellose sodium 0.5%, net price 30 × 0.4 mL = £5.75; 90 × 0.4 mL = £15.53; 1%, 30 × 0.4 mL = £3.00, 60 × 0.4 mL = £6.00

Celluvisc® (Allergan)

Eye drops, carmellose sodium 0.5%, net price 30 × 0.4 mL = £4.80, 90 × 0.4 mL = £15.53; 1%, 30 × 0.4 mL = £3.00, 60 × 0.4 mL = £10.99

Melophthal® (Martindale)

Eye drops, carmellose sodium 0.5%, net price 30 × 0.4 mL = £5.75; 1%, 30 × 0.4 mL = £3.00

Note Each unit is resealable and may be used for up to 12 hours

HYDROXYETHYLCELLULOSE**Indications and dose****Tear deficiency**

Apply as required

Minims® Artificial Tears (Bausch & Lomb)

Eye drops, hydroxyethylcellulose 0.44%, sodium chloride 0.35%, net price 20 × 0.5 mL = £8.97

HYPROMELLOSE**Indications and dose****Tear deficiency**

Apply as required

Note The Royal Pharmaceutical Society has stated that where it is not possible to ascertain the strength of hypromellose prescribed, the prescriber should be contacted to clarify the strength intended.

Hypromellose (Non-proprietary)

Eye drops, hypromellose 0.3%, net price 10 mL = £1.05

Excipients may include benzalkonium chloride

Brands include Lumecare® Hypromellose, Mandanol®

Artelac® (Bausch & Lomb)

Eye drops, hypromellose 0.32%, net price 10 mL = £4.99

Excipients include cetrimide, disodium edetate

Isopto Alkaline® (Alcon)

Eye drops, hypromellose 1%, net price 10 mL = 94p

Excipients include benzalkonium chloride

Isopto Plain® (Alcon)

Eye drops, hypromellose 0.5%, net price 10 mL = 81p

Excipients include benzalkonium chloride

Tear-Lac® (Scope Ophthalmics)

Eye drops, hypromellose 0.3%, net price 10 mL = £5.75

Tears Naturale® (Alcon)

Eye drops, hypromellose 0.3%, dextran '70' 0.1%, net price 15 mL = £1.89

Excipients include benzalkonium chloride, disodium edetate

▲ **Single use****Artelac**® SDU (Bausch & Lomb)

Eye drops, hypromellose 0.32%, net price 30 × 0.5 mL = £16.95, 60 × 0.5 mL = £32.85

Hydromoor® (Moorfields)

Eye drops, hypromellose 0.3%, net price 30 × 0.4 mL = £5.75

Lumecare® Preservative Free Tear Drops (Medicom)

Eye drops, hypromellose 0.3%, net price 30 × 0.5 mL = £5.72

Tears Naturale® Single Dose (Alcon)

Eye drops, hypromellose 0.3%, dextran '70' 0.1%, net price 28 × 0.4 mL = £13.26

LIQUID PARAFFIN**Indications and dose****Dry eye conditions**

Apply as required

Lacri-Lube® (Allergan)

Eye ointment, white soft paraffin 57.3%, liquid paraffin 42.5%, wool alcohols 0.2%, net price 3.5 g = £2.51, 5 g = £3.32

VitaA-POS® (Scope Ophthalmics)

Eye ointment, retinol palmitate 250 units/g, white soft paraffin, light liquid paraffin, liquid paraffin, wool fat, net price 5 g = £2.75

MACROGOLS

(Polyethylene glycols)

Indications and dose**Dry eye conditions**

Apply as required

Systane® (Alcon)

Eye drops, polyethylene glycol 400 0.4%, propylene glycol 0.3%, hydroxypropyl guar, net price 10 mL = £4.66

Systane® Ultra (Alcon)

Eye drops, polyethylene glycol 400 0.4%, propylene glycol 0.3%, hydroxypropyl guar, sorbitol, net price 10 mL = £6.69

▲ **Single use****Systane**® (Alcon)

Eye drops, polyethylene glycol 400 0.4%, propylene glycol 0.3%, hydroxypropyl guar, sorbitol, net price 28 × 0.8 mL = £4.66

Systane® Ultra (Alcon)

Eye drops, polyethylene glycol 400 0.4%, propylene glycol 0.3%, hydroxypropyl guar, sorbitol, net price 30 × 0.7 mL = £6.69

PARAFFIN, YELLOW, SOFT**Indications and dose**

See notes above

Apply 2 hourly as required

Simple Eye Ointment

Ointment, liquid paraffin 10%, wool fat 10%, in yellow soft paraffin, net price 4 g = £3.42

POLYVINYL ALCOHOL**Indications and dose****Tear deficiency**

Apply as required

Liquifilm Tears® (Allergan)

Ophthalmic solution (= eye drops), polyvinyl alcohol 1.4%, net price 15 mL = £1.93

Excipients include benzalkonium chloride, disodium edetate**Sno Tears®** (Bausch & Lomb)

Eye drops, polyvinyl alcohol 1.4%, net price 10 mL = £1.06

Excipients include benzalkonium chloride, disodium edetate**Single use****Liquifilm Tears®** (Allergan)

Ophthalmic solution (= eye drops), polyvinyl alcohol 1.4%, povidone 0.6%, net price 30 × 0.4 mL = £5.35

SODIUM CHLORIDE**Indications and dose****Irrigation, including first-aid removal of harmful substances**

Use as required

Sodium Chloride 0.9% Solutions

See section 13.11.1

Balanced Salt Solution (POM)

Solution (sterile), sodium chloride 0.64%, sodium acetate 0.39%, sodium citrate 0.17%, calcium chloride 0.048%, magnesium chloride 0.03%, potassium chloride 0.075%

For intra-ocular or topical irrigation during surgical procedures

Single use**Minimis® Saline** (Bausch & Lomb)

Eye drops, sodium chloride 0.9%, net price 20 × 0.5 mL = £7.14

SODIUM HYALURONATE**Indications and dose****Dry eye conditions**

Apply as required

Artelac Rebalance® (Bausch & Lomb)

Eye drops, sodium hyaluronate 0.15%, net price 10 mL = £4.00

Blink® Intensive Tears (AMO)

Eye drops, sodium hyaluronate 0.2%, polyethylene glycol 400 0.25%, net price 10 mL = £2.97

Hyabak® (Spectrum Thea)

Eye drops, sodium hyaluronate 0.15%, net price 10 mL = £7.99

Hylo-Care® (Scope Ophthalmics)

Eye drops, sodium hyaluronate 0.1%, dexpantenol 2%, net price 10 mL = £10.30

Hylo-Forte® (Scope Ophthalmics)

Eye drops, sodium hyaluronate 0.2%, net price 10 mL = £9.50

Hylo-Tear® (Scope Ophthalmics)

Eye drops, sodium hyaluronate 0.1%, net price 10 mL = £8.50

Lumecare® Sodium Hyaluronate (Medicom)

Eye drops, sodium hyaluronate 0.15%, net price 10 mL = £3.97

Oxyl® (Kestrel Ophthalmics)

Eye drops, sodium hyaluronate 0.15%, net price 10 mL = £4.15

Vismed® Gel Multi (TRB Chemedica)

Eye drops, sodium hyaluronate 0.3%, net price 10 mL = £7.95

Vismed® Multi (TRB Chemedica)

Eye drops, sodium hyaluronate 0.18%, net price 10 mL = £6.81

Single use**Artelac® Splash** (Bausch & Lomb)

Eye drops, sodium hyaluronate 0.2%, net price 30 × 0.5 mL = £7.00, 60 × 0.5 mL = £11.50

Blink® Intensive Tears (AMO)

Eye drops, sodium hyaluronate 0.2%, polyethylene glycol 400 0.25%, net price 20 × 0.4 mL = £2.97

Clinitas® (Altacor)

Eye drops, sodium hyaluronate 0.4%, net price 30 × 0.5 mL = £5.70

Note Each unit is resealable and may be used for up to 12 hours after first opening**Lubristil®** (Moorfields)

Eye drops, sodium hyaluronate 0.15%, net price 20 × 0.3 mL = £4.99

Lubristil® Gel (Moorfields)

Eye drops, sodium hyaluronate 0.15%, xanthan gum 1%, net price 20 × 0.4 mL = £6.49

Ocusan® (Agepha)

Eye drops, sodium hyaluronate 0.2%, net price 20 × 0.5 mL = £5.31

Vismed® (TRB Chemedica)

Eye drops, sodium hyaluronate 0.18%, net price 20 × 0.3 mL = £5.10

Vismed® Gel (TRB Chemedica)

Eye drops, sodium hyaluronate 0.3%, net price 20 × 0.45 mL = £5.98

SOYBEAN OIL**Indications and dose****Dry eye conditions**

Apply up to 4 times a day

Emustil® (Moorfields)

Eye drops, soybean oil 7%, natural phospholipids 3%, net price 20 × 0.3 mL = £6.22

11.8.2 Ocular diagnostic and peri-operative preparations

Ocular diagnostic preparations

Fluorescein sodium is used in diagnostic procedures and for locating damaged areas of the cornea due to injury or disease.

FLUORESCIN SODIUM

Indications and dose

Detection of lesions and foreign bodies

Sufficient to stain damaged areas

Minims® Fluorescein Sodium (Bausch & Lomb)

Eye drops, fluorescein sodium 1% or 2%, net price $20 \times 0.5 \text{ mL (both)} = \text{£}8.52$

With local anaesthetic

Section 11.7

Ocular peri-operative drugs

Drugs used to prepare the eye for surgery and drugs that are injected into the anterior chamber at the time of surgery are included here.

Sodium hyaluronate is used during surgical procedures on the eye.

Apraclonidine, an α_2 -adrenoceptor agonist, reduces intra-ocular pressure possibly by reducing the production of aqueous humour. It is used for short-term treatment only.

Balanced Salt Solution is used routinely in intra-ocular surgery (section 11.8.1).

ACETYLCHOLINE CHLORIDE

Cautions gastro-intestinal spasm, peptic ulcer; heart failure; asthma; hyperthyroidism; urinary-tract obstruction

Pregnancy avoid unless potential benefit outweighs risk—no information available

Breast-feeding avoid unless potential benefit outweighs risk—no information available

Licensed use not licensed for use in children

Indications and dose

Cataract surgery, penetrating keratoplasty, iridectomy, other anterior segment surgery requiring rapid complete miosis

Consult product literature

Miochol-E® (Bausch & Lomb) (PoM)

Intra-ocular irrigation, powder for reconstitution, acetylcholine chloride 10 mg/mL (1%) when reconstituted, net price 20-mg vial (with solvent) = £7.28

Miphtel® (SD Healthcare) (PoM)

Intra-ocular irrigation, powder for reconstitution, acetylcholine chloride 10 mg/mL (1%) when reconstituted, net price 20-mg vial (with solvent) = £7.28

APRACLONIDINE

Note Apraclonidine is a derivative of clonidine

Cautions history of angina, severe coronary insufficiency, recent myocardial infarction, heart failure, cerebrovascular disease, vasovagal attack, hypertension; Raynaud's syndrome; thromboangiitis obli-

terans; depression; monitor intra-ocular pressure and visual fields; loss of effect may occur over time; suspend treatment if reduction in vision occurs in end-stage glaucoma; monitor for excessive reduction in intra-ocular pressure following peri-operative use; **interactions:** Appendix 1 (α_2 -adrenoceptor stimulants)

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving)

Contra-indications history of severe or unstable and uncontrolled cardiovascular disease

Hepatic impairment manufacturer advises caution

Renal impairment use with caution in chronic renal failure

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects taste disturbance, conjunctivitis, dry eye, ocular intolerance (withdraw if eye pruritus, ocular hyperaemia, increased lacrimation, or oedema of the eyelids and conjunctiva occur), rhinitis; *less commonly* chest pain, asthma, dyspnoea, throat irritation, nervousness, irritability, impaired co-ordination, myalgia, mydriasis, keratitis, keratopathy, photophobia, visual impairment, corneal erosion and infiltrates, blepharospasm, blepharitis, eyelid ptosis or retraction, conjunctival vascular disorders, rhinorrhoea, parosmia; since absorption may follow topical application, systemic effects (see Clonidine, section 2.5.2) may occur

Licensed use 0.5% drops not licensed for use in children under 12 years; 1% drops not licensed for use in children

Indications and dose

See preparations below

lopidine® (Alcon) (PoM)

Ophthalmic solution (= eye drops), apraclonidine 1% (as hydrochloride), net price 12×2 single use 0.25-mL units = £77.81

Dose

Control or prevention of postoperative elevation of intra-ocular pressure after anterior segment laser surgery

Apply 1 drop 1 hour before laser procedure then 1 drop immediately after completion of procedure

Ophthalmic solution (= eye drops), apraclonidine 0.5% (as hydrochloride), net price 5 mL = £10.88

Excipients include benzalkonium chloride

Dose

Short-term adjunctive treatment of chronic glaucoma in patients not adequately controlled by another drug (see note below)

Child 12–18 years apply 1 drop 3 times daily usually for max. 1 month

Note May not provide additional benefit if patient already using two drugs that suppress the production of aqueous humour

DICLOFENAC SODIUM

Licensed use not licensed for use in children

Indications and dose

Inhibition of intra-operative miosis during cataract surgery (but does not possess intrinsic mydriatic properties), postoperative inflammation in cataract surgery, strabismus surgery, argon laser trabeculoplasty

Consult product literature

Voltarol® Ophtha Multidose (Spectrum Thea) (PoM)

Eye drops, diclofenac sodium 0.1%, net price 5 mL = £6.68

Excipients include benzalkonium chloride, disodium edetate, propylene glycol

Single use

Voltarol® Ophtha (Spectrum Thea) (PoM)

Eye drops, diclofenac sodium 0.1%, net price pack of 5 single-dose units = £4.00, 40 single-dose units = £32.00

FLURBIPROFEN SODIUM

Licensed use not licensed for use in children

Indications and dose

Inhibition of intra-operative miosis (but does not possess intrinsic mydriatic properties), control of postoperative and post-laser trabeculoplasty inflammation (if corticosteroids contra-indicated)

Consult product literature

Ocufen® (Allergan) (PoM)

Ophthalmic solution (= eye drops), flurbiprofen sodium 0.03%, polyvinyl alcohol (*Liquifilm*®) 1.4%, net price 40 × 0.4 mL = £37.15

KETOROLAC TROMETAMOL

Licensed use not licensed for use in children

Indications and dose

Prophylaxis and reduction of inflammation and associated symptoms following ocular surgery

Consult product literature

Acular® (Allergan) (PoM)

Eye drops, ketorolac trometamol 0.5%, net price 5 mL = £3.00

Excipients include benzalkonium chloride, disodium edetate

lenses (including frequently replaced lenses) and should be treated by specialists.

Contact lenses and drug treatment Special care is required in prescribing eye preparations for contact lens users. Some drugs and preservatives in eye preparations can accumulate in hydrogel lenses and can cause adverse reactions. Therefore, unless medically indicated, the lenses should be removed before instillation of the eye preparation and not worn during the period of treatment. Alternatively, unpreserved drops can be used. Eye drops may, however, be instilled while patients are wearing rigid corneal contact lenses. Ointment preparations should never be used in conjunction with contact lens wear; oily eye drops should also be avoided.

Many drugs given systemically can also have adverse effects on contact lens wear. These include oral contraceptives (particularly those with a higher oestrogen content), drugs which reduce blink rate (e.g. anxiolytics, hypnotics, antihistamines, and muscle relaxants), drugs which reduce lacrimation (e.g. antihistamines, antimuscarinics, phenothiazines and related drugs, some beta-blockers, diuretics, and tricyclic antidepressants), and drugs which increase lacrimation (including ephedrine and hydalazine). Other drugs that can affect contact lens wear are isotretinoin (can cause conjunctival inflammation), aspirin (salicylic acid appears in tears and can be absorbed by contact lenses—leading to irritation), and rifampicin and sulfasalazine (can discolour lenses).

11.9 Contact lenses

Some children and adolescents prefer to wear contact lenses rather than spectacles for both cosmetic and medical reasons. Visual defects are corrected by either rigid ('hard' or gas permeable) lenses or soft (hydrogel) lenses; soft lenses are the most popular type, because they are initially the most comfortable, but they may not give the best vision. Lenses should usually be worn for a specified number of hours each day and removed for sleeping. The risk of infectious and non-infectious keratitis is increased by extended continuous contact lens wear in children, which is not recommended, except when medically indicated.

Contact lenses require meticulous care. Poor compliance with directions for use, and with daily cleaning and disinfection, can result in complications including ulcerative keratitis or conjunctivitis. One-day disposable lenses, which are worn only once and therefore require no disinfection or cleaning, are becoming increasingly popular.

Acanthamoeba keratitis, a painful and sight-threatening condition, is associated with ineffective lens cleaning and disinfection, the use of contaminated lens cases, or tap water coming into contact with the lenses. The condition is especially associated with the use of soft

12 Ear, nose, and oropharynx

12.1	Drugs acting on the ear	541
12.1.1	Otitis externa	541
12.1.2	Otitis media	544
12.1.3	Removal of ear wax	544
12.2	Drugs acting on the nose	545
12.2.1	Drugs used in nasal allergy	545
12.2.2	Topical nasal decongestants	548
12.2.3	Nasal preparations for infection	549
12.3	Drugs acting on the oropharynx	549
12.3.1	Drugs for oral ulceration and inflammation	549
12.3.2	Oropharyngeal anti-infective drugs	551
12.3.3	Lozenges and sprays	552
12.3.4	Mouthwashes and gargles	553
12.3.5	Treatment of dry mouth	554

This chapter also includes advice on the drug management of the following:

- allergic rhinitis, p. 545
- nasal polyps, p. 545
- oropharyngeal infections, p. 551
- periodontitis, p. 550

12.1 Drugs acting on the ear

12.1.1	Otitis externa
12.1.2	Otitis media
12.1.3	Removal of ear wax

12.1.1 Otitis externa

Otitis externa is an inflammatory reaction of the lining of the ear canal usually associated with an underlying seborrhoeic dermatitis or eczema; it is important to exclude an underlying chronic otitis media before treatment is commenced. Many cases recover after thorough cleansing of the external ear canal by suction or dry mopping.

A frequent problem in resistant cases is the difficulty in applying lotions and ointments satisfactorily to the relatively inaccessible affected skin. The most effective method is to introduce a ribbon gauze dressing or sponge wick soaked with **corticosteroid** ear drops or with an astringent such as **aluminium acetate** solution. When this is not practical, the ear should be gently cleansed with a probe covered in cotton wool and the patient encouraged to lie with the affected ear uppermost for ten minutes after the canal has been filled with a liberal quantity of the appropriate solution.

Secondary infection in otitis externa may be of bacterial, fungal, or viral origin. If infection is present, a topical anti-infective which is not used systemically (such as **neomycin** or **clioquinol**) may be used, but for only about a week because excessive use may result in fungal infections that are difficult to treat. Sensitivity to the anti-infective or solvent may occur and resistance to antibacterials is a possibility with prolonged use. **Aluminium acetate** ear drops are also effective against bacterial infection and inflammation of the ear. **Chloramphenicol** may be used, but the ear drops contain propylene glycol and cause hypersensitivity reactions in about 10% of patients. Solutions containing an anti-infective and a corticosteroid (such as *Locorten-Vioform*®) are used for treating children when infection is present with inflammation and eczema. **Clotrimazole** 1% solution is used topically to treat fungal infection in otitis externa.

In view of reports of ototoxicity, manufacturers contraindicate treatment with topical **aminoglycosides** or **polymyxins** in children with a perforated tympanic membrane (eardrum) or patent grommet. However, some specialists do use these drops cautiously in the presence of a perforation or patent grommet in children with chronic suppurative otitis media (section 12.1.2) and when other measures have failed for otitis externa; treatment should be considered only by specialists in the following circumstances:

- drops should only be used in the presence of obvious infection;
- treatment should be for no longer than 2 weeks;

- the carer and child should be counselled on the risk of ototoxicity and given justification for the use of these topical antibiotics;
- baseline audiometry should be performed, if possible, before treatment is commenced.

Clinical expertise and judgement should be used to assess the risk of treatment versus the benefit to the patient in such circumstances.

A solution of **acetic acid** 2% acts as an antifungal and antibacterial in the external ear canal and may be used to treat mild otitis externa. More severe cases require treatment with an anti-inflammatory preparation with or without an anti-infective drug. A proprietary preparation containing acetic acid 2% (*EarCalm*® spray) is on sale to the public for children over 12 years.

For severe pain associated with otitis externa, a simple analgesic, such as **paracetamol** (section 4.7.1) or **ibuprofen** (section 10.1.1), can be used. A systemic antibacterial (Table 1, section 5.1) can be used if there is spreading cellulitis or if the child is systemically unwell. When a resistant staphylococcal infection (a boil) is present in the external auditory canal, oral **flucloxacillin** (section 5.1.1.2) is the drug of choice; oral **ciprofloxacin** (section 5.1.12) or a systemic aminoglycoside may be needed for pseudomonal infections, particularly in children with diabetes or compromised immunity.

The skin of the pinna adjacent to the ear canal is often affected by eczema. A topical corticosteroid (section 13.4) cream or ointment is then required, but prolonged use should be avoided.

Administration To administer ear drops, lay the child down with the head turned to one side; for an infant pull the earlobe back and down, for an older child pull the earlobe back and up.

Astringent preparations

ALUMINIUM ACETATE

Licensed use not licensed

Indications and dose

Inflammation in otitis externa (see notes above)

Insert into meatus or apply on a ribbon gauze dressing or sponge wick which should be kept saturated with the ear drops

Aluminium Acetate (Non-proprietary)

Ear drops 13%, aluminium sulfate 2.25 g, calcium carbonate 1 g, tartaric acid 450 mg, acetic acid (33%) 2.5 mL, purified water 7.5 mL
Available as manufactured special

Ear drops 8%, dilute 8 parts aluminium acetate ear drops (13%) with 5 parts purified water. Must be freshly prepared

Anti-inflammatory preparations

Corticosteroids

Topical corticosteroids are used to treat inflammation and eczema in otitis externa.

Cautions Prolonged use of topical corticosteroid ear preparations should be avoided.

Contra-indications Corticosteroid ear preparations should be avoided in the presence of an untreated ear

infection. If infection is present, the corticosteroid should be used in combination with a suitable anti-infective (see notes above).

Side-effects Local sensitivity reactions may occur.

BETAMETHASONE SODIUM PHOSPHATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturers)

Indications and dose

Eczematous inflammation in otitis externa (see notes above); for dose, see under preparations

Eye section 11.4.1

Nose section 12.2.1 and section 12.2.3

Betnesol® (RPH) (PoM)

Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%. Net price 10 mL = £2.32

Excipients include benzalkonium chloride, disodium edetate

Dose

ear, instil 2–3 drops every 2–3 hours; reduce frequency when relief obtained

Vistamethasone® (Martindale) (PoM)

Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%. Net price 5 mL = £1.02; 10 mL = £1.16

Excipients include benzalkonium chloride, disodium edetate

Dose

ear, instil 2–3 drops every 3–4 hours; reduce frequency when relief obtained

■ **With antibacterial**

Betnesol-N® (RPH) (PoM)

Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%, neomycin sulfate 0.5%. Net price 10 mL = £2.39

Excipients include benzalkonium chloride, disodium edetate

Dose

ear, instil 2–3 drops 3–4 times daily

DEXAMETHASONE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use *Sofradex*® licensed for use in children (age range not specified by manufacturers)

Indications and dose

Eczematous inflammation in otitis externa (see notes above); for dose, see under preparations

■ **With antibacterial**

Otomize® (Forest) (PoM)

Ear spray, dexamethasone 0.1%, neomycin sulfate 3250 units/mL, glacial acetic acid 2%. Net price 5-mL pump-action aerosol unit = £3.50

Excipients include hydroxybenzoates (parabens)

Dose

Child 2–18 years ear, apply 1 metered spray 3 times daily

Sofradex® (Sanofi-Aventis) (PoM) 

Drops (for ear or eye), dexamethasone (as sodium metasulfobenzoate) 0.05%, framycetin sulfate 0.5%, gramicidin 0.005%. Net price 10 mL = £6.25

Excipients include polysorbate 80

Dose

ear, instil 2–3 drops 3–4 times daily; eye, section 11.4.1

FLUMETASONE PIVALATE

(Flumethasone Pivalate)

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Indications and dose

Eczematous inflammation in otitis externa (see notes above); for dose, see under preparation

With antibacterial**Locorten-Vioform®** (AMCo) (PoM) 

Ear drops, flumetasone pivalate 0.02%, clioquinol 1%. Net price 7.5 mL = £1.76

Contra-indications iodine sensitivity

Dose

Child 2–18 years instil 2–3 drops into the ear twice daily for 7–10 days

Note Clioquinol stains skin and clothing

HYDROCORTISONE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Indications and dose

Eczematous inflammation in otitis externa (see notes above); for dose, see under preparations

With antibacterial**Gentisone® HC** (AMCo) (PoM) 

Ear drops, hydrocortisone acetate 1%, gentamicin 0.3% (as sulfate). Net price 10 mL = £4.76

Excipients include benzalkonium chloride, disodium edetate

Dose

ear, instil 2–4 drops 3–4 times daily and at night

PREDNISOLONE SODIUM PHOSPHATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturers)

Indications and dose

Eczematous inflammation in otitis externa (see notes above); for dose, see under preparations

Eye section 11.4.1

Predsol® (RPH) (PoM) 

Drops (for ear or eye), prednisolone sodium phosphate 0.5%. Net price 10 mL = £2.00

Excipients include benzalkonium chloride, disodium edetate

Dose

ear, instil 2–3 drops every 2–3 hours; reduce frequency when relief obtained

Anti-infective preparations**CHLORAMPHENICOL** 

Cautions avoid prolonged use (see notes above)

Side-effects high incidence of sensitivity reactions to vehicle

Licensed use licensed for use in children (age range not specified by manufacturers)

Indications and dose

Bacterial infection in otitis externa (but see notes above); for dose, see under preparation

Chloramphenicol (Non-proprietary) (PoM) 

Ear drops, chloramphenicol in propylene glycol, net price 5%, 10 mL = £33.40; 10%, 10 mL = £19.52

Excipients include propylene glycol

Dose

ear, instil 2–3 drops 2–3 times daily

CLOTRIMAZOLE

Side-effects occasional local irritation or sensitivity

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Fungal infection in otitis externa (see notes above); for dose, see under preparation

Canesten® (Bayer Consumer Care)

Solution, clotrimazole 1% in polyethylene glycol 400 (macrogol 400). Net price 20 mL = £2.30

Dose

ear, apply 2–3 times daily continuing for at least 14 days after disappearance of infection

FRAMYCETIN SULFATE

Cautions avoid prolonged use (see notes above)

Contra-indications perforated tympanic membrane (see p. 541)

Side-effects local sensitivity

Indications and dose

Bacterial infection in otitis externa (see notes above)

Eye section 11.3.1

With corticosteroid

Sofradex® see Dexamethasone, p. 543

GENTAMICIN

Cautions avoid prolonged use (see notes above)

Contra-indications perforated tympanic membrane (but see p. 541 and section 12.1.2)

Side-effects local sensitivity

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Bacterial infection in otitis externa (see notes above); for dose, see under preparations

Gentamicin® (AMCo) (PoM)

Drops (for ear or eye), gentamicin 0.3% (as sulfate).

Net price 10 mL = £2.13

Excipients include benzalkonium chloride

Dose

ear, instil 2–3 drops 3–4 times daily and at night; eye, section 11.3.1

■ **With corticosteroid****Gentisone**® HC see Hydrocortisone, p. 543**NEOMYCIN SULFATE****Cautions** avoid prolonged use (see notes above)**Contra-indications** perforated tympanic membrane (see p. 541)**Side-effects** local sensitivity**Indications and dose****Bacterial infection in otitis externa** (see notes above)■ **With corticosteroid****Betnesol-N**® (PoM) see Betamethasone, p. 542**Otomize**® see Dexamethasone, p. 542**12.1.2 Otitis media**

Acute otitis media Acute otitis media is the commonest cause of severe aural pain in young children and may occur with even minor upper respiratory tract infections. Children diagnosed with acute otitis media should not be prescribed antibacterials routinely as many infections, especially those accompanying coryza, are caused by viruses. Most uncomplicated cases resolve without antibacterial treatment and a **simple analgesic**, such as paracetamol, may be sufficient. In children without systemic features, a **systemic antibacterial** (Table 1, section 5.1) may be started after 72 hours if there is no improvement, or earlier if there is deterioration, if the child is systemically unwell, if the child is at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis), if mastoiditis is present, or in children under 2 years of age with bilateral otitis media. Perforation of the tympanic membrane in children with *acute otitis media* usually heals spontaneously without treatment; if there is no improvement, e.g. pain or discharge persists, a systemic antibacterial (Table 1, section 5.1) can be given. Topical antibacterial treatment of acute otitis media is ineffective and there is no place for ear drops containing a local anaesthetic.

Otitis media with effusion Otitis media with effusion (glue ear) occurs in about 10% of children and in 90% of children with cleft palates. Antimicrobials, corticosteroids, decongestants, and antihistamines have little place in the routine management of otitis media with effusion. If glue ear persists for more than a month or two, the child should be referred for assessment and follow up because of the risk of long-term hearing impairment which can delay language development. Untreated or resistant glue ear may be responsible for some types of *chronic otitis media*.

Chronic otitis media Opportunistic organisms are often present in the debris, keratin, and necrotic bone of the middle ear and mastoid in children with chronic otitis media. The mainstay of treatment is thorough

cleansing with aural microsuction, which may completely resolve long-standing infection. Cleansing may be followed by topical treatment as for otitis externa (section 12.1.1); this is particularly beneficial for discharging ears or infections of the mastoid cavity. Acute exacerbations of chronic infection may require treatment with an oral antibacterial (Table 1, section 5.1); a swab should be taken to identify infecting organisms and antibacterial sensitivity.

In view of reports of ototoxicity, manufacturers contraindicate topical treatment with ototoxic antibacterials in the presence of a tympanic perforation or patent grommet. **Ciprofloxacin** or **ofloxacin** eye drops used in the ear [unlicensed use] or ear drops [both unlicensed; available from 'special-order' manufacturers or specialist importing companies, see p. 840] are an effective alternative to such ototoxic ear drops for chronic otitis media in patients with perforation of the tympanic membrane.

However, some specialists do use ear drops containing **aminoglycosides** or **polymyxins** [unlicensed indications] cautiously in children with chronic suppurative otitis media and perforation of the tympanic membrane, if the otitis media has failed to settle with systemic antibacterials; treatment should be considered only by **specialists** in the following circumstances:

- drops should only be used in the presence of obvious infection;
- treatment should be for no longer than 2 weeks;
- the carer and child should be counselled on the risk of ototoxicity and given justification for the use of these topical antibiotics;
- baseline audiometry should be performed, if possible, before treatment is commenced.

Clinical expertise and judgement should be used to assess the risk of treatment versus the benefit to the patient in such circumstances. It is considered that the pus in the middle ear associated with otitis media also carries a risk of ototoxicity.

12.1.3 Removal of ear wax

Ear wax (cerumen) is a normal bodily secretion which provides a protective film on the meatal skin and need only be removed if it causes hearing loss or interferes with a proper view of the ear drum.

Ear wax causing discomfort or impaired hearing may be softened with simple remedies such as **olive oil** ear drops or **almond oil** ear drops; **sodium bicarbonate** ear drops are also effective, but may cause dryness of the ear canal. If the wax is hard and impacted, the drops can be used twice daily for several days and this may reduce the need for mechanical removal of the wax. The child should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear. Proprietary preparations containing organic solvents can irritate the meatal skin, and in most cases the simple remedies indicated above are just as effective and less likely to cause irritation. Docusate sodium or urea hydrogen peroxide are ingredients in a number of proprietary preparations for softening ear wax.

If necessary, wax may be removed by irrigation with water (warmed to body temperature). Ear irrigation is generally best avoided in young children, in children

unable to co-operate with the procedure, in children who have had otitis media in the last 6 weeks, in otitis externa, in children with cleft palate, a history of ear drum perforation, or previous ear surgery. A child who has hearing in one ear only should not have that ear irrigated because even a very slight risk of damage is unacceptable in this situation.

For administration of ear drops, see p. 542.

Almond Oil (Non-proprietary)

Ear drops, almond oil in a suitable container
Allow to warm to room temperature before use

Olive Oil (Non-proprietary)

Ear drops, olive oil in a suitable container
Allow to warm to room temperature before use

Sodium Bicarbonate (Non-proprietary)

Ear drops, sodium bicarbonate 5%, net price 10 mL = £1.25

Cerumol[®] (Thornton & Ross)

Ear drops, chlorobutanol 5%, arachis (peanut) oil 57.3%. Net price 11 mL = £1.99

Exterol[®] (Dermal)

Ear drops, urea–hydrogen peroxide complex 5% in glycerol. Net price 8 mL = £1.75

Molcer[®] (Wallace Mfg)

Ear drops, docusate sodium 5%. Net price 15 mL = £8.08
Excipients include propylene glycol

Otex[®] (DDD)

Ear drops, urea–hydrogen peroxide 5%. Net price 8 mL = £2.89

Waxsol[®] (Meda)

Ear drops, docusate sodium 0.5%. Net price 10 mL = £1.95

12.2.1 Drugs used in nasal allergy

Mild allergic rhinitis is controlled by **antihistamines** (see also section 3.4.1) or topical **nasal corticosteroids**; systemic nasal decongestants (section 3.10) are not recommended for use in children. Topical nasal decongestants can be used for a short period to relieve congestion and allow penetration of a topical nasal corticosteroid.

More persistent symptoms can be relieved by topical nasal **corticosteroids**; **sodium cromoglicate** is an alternative, but may be less effective. The topical antihistamine, **azelastine**, is useful for controlling breakthrough symptoms in allergic rhinitis. Azelastine is less effective than nasal corticosteroids, but probably more effective than sodium cromoglicate. In seasonal allergic rhinitis (e.g. hay fever), treatment should begin 2 to 3 weeks before the season commences and may have to be continued for several months; continuous long-term treatment may be required in perennial rhinitis.

Montelukast (section 3.3.2) is less effective than topical nasal corticosteroids; montelukast can be used in children with seasonal allergic rhinitis (unresponsive to other treatments) and concomitant asthma.

Children with disabling symptoms of seasonal rhinitis (e.g. students taking important examinations), may be treated with oral **corticosteroids** (section 6.3.2) for short periods. Oral corticosteroids may also be used at the beginning of a course of treatment with a corticosteroid spray to relieve severe mucosal oedema and allow the spray to penetrate the nasal mucosa.

Sometimes allergic rhinitis is accompanied by vasomotor rhinitis. In this situation, the addition of topical nasal **ipratropium bromide** (section 12.2.2) can reduce watery rhinorrhoea.

Pregnancy If a pregnant woman cannot tolerate the symptoms of allergic rhinitis, treatment with nasal beclometasone, budesonide, fluticasone propionate, or sodium cromoglicate may be considered.

12.2 Drugs acting on the nose

12.2.1 Drugs used in nasal allergy

12.2.2 Topical nasal decongestants

12.2.3 Nasal preparations for infection

Rhinitis is often self-limiting but bacterial sinusitis may require treatment with antibacterials (Table 1, section 5.1). Many nasal preparations contain sympathomimetic drugs (section 12.2.2) which can give rise to rebound congestion (*rhinitis medicamentosa*) and may damage the nasal cilia. **Sodium chloride** 0.9% solution may be used as a douche or 'sniff' following endonasal surgery.

Administration To administer nasal drops, lay the child face-upward with the neck extended, instil the drops, then sit the child up and tilt the head forward.

Nasal polyps Short-term use of corticosteroid nasal drops helps to shrink nasal polyps; to be effective, the drops must be administered with the child in the 'head down' position. A short course of a systemic corticosteroid (section 6.3.2) may be required initially to shrink large polyps. A corticosteroid nasal spray can be used to maintain the reduction in swelling and also for the initial treatment of small polyps.

Antihistamines

AZELASTINE HYDROCHLORIDE

Side-effects irritation of nasal mucosa; bitter taste (if applied incorrectly); very rarely hypersensitivity reactions including rash, pruritus, and urticaria

Indications and dose

Treatment of allergic rhinitis for dose, see under preparation

Rhinolast[®] (Meda)

Nasal spray, azelastine hydrochloride 140 micrograms (0.14 mL)/metered spray. Net price 22 mL (157-spray unit with metered pump) = £10.45
Excipients include sodium edetate

Dose

Child 5–18 years apply 140 micrograms (1 spray) into each nostril twice daily

Note Preparations of azelastine hydrochloride can be sold to the public for nasal administration in aqueous form (other than by aerosol) for the treatment of seasonal allergic rhinitis or perennial allergic rhinitis in children over 5 years, subject to max. single dose of 140 micrograms per nostril, max. daily dose of 280 micrograms per nostril, and a pack size limit of 36 doses

Corticosteroids

Nasal preparations containing corticosteroids have a useful role in the prophylaxis and treatment of allergic rhinitis (see notes above). They are also used for the symptomatic treatment of adenoidal hypertrophy.

Cautions Corticosteroid nasal preparations should be avoided in the presence of untreated nasal infections, and also after nasal surgery (until healing has occurred); they should also be avoided in pulmonary tuberculosis. Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged; for cautions and side-effects of systemic corticosteroids, see section 6.3.2. The risk of systemic effects may be greater with nasal drops than with nasal sprays; drops are administered incorrectly more often than sprays. The height of children receiving prolonged treatment with nasal corticosteroids should be monitored; if growth is slowed, referral to a paediatrician should be considered.

Side-effects Local side-effects include dryness, irritation of nose and throat, and epistaxis. Nasal ulceration has been reported, and occurs commonly with nasal preparations containing fluticasone furoate or mometasone furoate. Nasal septal perforation (usually following nasal surgery) occurs very rarely. Raised intra-ocular pressure or glaucoma may occur rarely. Headache, smell and taste disturbances may also occur. Hyperactivity, sleep disturbances, anxiety, depression, and aggression have been reported. Hypersensitivity reactions, including bronchospasm, have also been reported.

BECLOMETASONE DIPROPIONATE (Beclomethasone Dipropionate)

Cautions see notes above

Side-effects see notes above

Indications and dose

Prophylaxis and treatment of allergic and vasomotor rhinitis

Child 6–18 years apply 100 micrograms (2 sprays) into each nostril twice daily; max. total 400 micrograms (8 sprays) daily; when symptoms controlled, dose reduced to 50 micrograms (1 spray) into each nostril twice daily

Beclometasone (Non-proprietary) (PoM)

Nasal spray, beclometasone dipropionate 50 micrograms/metered spray. Net price 200-spray unit = £2.12

Brands include *Nasobec Aqueous*®

Beconase® (A&H) (PoM)

Nasal spray (aqueous suspension), beclometasone dipropionate 50 micrograms/metered spray. Net price 200-spray unit with applicator = £2.19

Excipients include benzalkonium chloride, polysorbate 80

BETAMETHASONE SODIUM PHOSPHATE

Cautions see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Non-infected inflammatory conditions of nose for dose, see under preparations

Eye section 11.4.1

Ear section 12.1.1

Betnesol® (RPH) (PoM)

Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%, net price 10 mL = £2.32

Excipients include benzalkonium chloride, disodium edetate

Dose

nose, instil 2–3 drops into each nostril 2–3 times daily

Vistamethasone® (Martindale) (PoM)

Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%. Net price 5 mL = £1.02, 10 mL = £1.16

Excipients include benzalkonium chloride, disodium edetate

Dose

nose, instil 2–3 drops into each nostril twice daily

BUDESONIDE

Cautions see notes above; **interactions:** Appendix 1 (corticosteroids)

Side-effects see notes above

Indications and dose

See under preparations

Budesonide (Non-proprietary) (PoM)

Nasal spray, budesonide 100 micrograms/metered spray, net price 100-spray unit = £5.90

Dose

Prophylaxis and treatment of allergic and vasomotor rhinitis

Child 12–18 years apply 200 micrograms (2 sprays) into each nostril once daily in the morning or 100 micrograms (1 spray) into each nostril twice daily; when control achieved reduce to 100 micrograms (1 spray) into each nostril once daily

Nasal polyps

Child 12–18 years apply 100 micrograms (1 spray) into each nostril twice daily for up to 3 months

Rhinocort Aqua® (AstraZeneca) (PoM)

Nasal spray, budesonide 64 micrograms/metered spray. Net price 120-spray unit = £3.49

Excipients include disodium edetate, polysorbate 80, potassium sorbate

Dose

Rhinitis

Child 12–18 years 128 micrograms (2 sprays) into each nostril once daily in the morning or 64 micrograms (1 spray) into each nostril twice daily; when control achieved reduce to 64 micrograms (1 spray) into each nostril once daily; max. duration of treatment 3 months

Nasal polyps

Child 12–18 years 64 micrograms (1 spray) into each nostril twice daily for up to 3 months

FLUTICASONE PROPIONATE

Cautions see notes above; **interactions:** Appendix 1 (corticosteroids)

Side-effects see notes above

Indications and dose**Prophylaxis and treatment of allergic rhinitis**

Child 4–12 years 50 micrograms (1 spray) into each nostril once daily, preferably in the morning, increased to max. twice daily if required

Child 12–18 years 100 micrograms (2 sprays) into each nostril once daily, preferably in the morning, increased to max. twice daily if required; when control achieved reduce to 50 micrograms (1 spray) into each nostril once daily

Nasal polyps see *Flixonase Nasule*® below

Flixonase® (A&H) (PoM)

Aqueous nasal spray, fluticasone propionate 50 micrograms/metered spray. Net price 150-spray unit with applicator = £11.01

Excipients include benzalkonium chloride, polysorbate 80

Flixonase Nasule® (A&H) (PoM)

Nasal drops, fluticasone propionate 400 micrograms/unit dose, net price 28 × 0.4-mL units = £12.99

Excipients include polysorbate 20

Dose**Nasal polyps**

Child 16–18 years instil 200 micrograms (approx. 6 drops) into each nostril once or twice daily; consider alternative treatment if no improvement after 4–6 weeks

Nasofan® (TEVA UK) (PoM)

Aqueous nasal spray, fluticasone propionate 50 micrograms/metered spray. Net price 150-spray unit = £8.04

Excipients include benzalkonium chloride, polysorbate 80

■ With azelastine hydrochloride**Dymista**® (Meda) (PoM)

Nasal spray, fluticasone propionate 50 micrograms, azelastine hydrochloride 137 micrograms/metered spray, net price 120-spray unit = £18.91

Excipients include benzalkonium chloride, polysorbate 80

Dose

Moderate to severe seasonal and perennial allergic rhinitis, if monotherapy with antihistamine or corticosteroid is inadequate

Child 12–18 years 1 spray into each nostril twice daily

■ Fluticasone furoate**Avamys**® (GSK) (PoM)

Nasal spray, fluticasone furoate 27.5 micrograms/metered spray, net price 120-spray unit = £6.44

Excipients include benzalkonium chloride, disodium edetate, polysorbate 80

Dose**Prophylaxis and treatment of allergic rhinitis**

- Child 6–12 years** 27.5 micrograms (1 spray) into each nostril once daily, increased if necessary to 55 micrograms (2 sprays) into each nostril once daily; when control achieved reduce to 27.5 micrograms (1 spray) into each nostril once daily

- Child 12–18 years** 55 micrograms (2 sprays) into each nostril once daily; when control achieved reduce to minimum effective dose, 27.5 micrograms (1 spray) into each nostril once daily may be sufficient

MOMETASONE FUROATE

Cautions see notes above

Side-effects see notes above

Indications and dose

See under preparation

Nasonex® (MSD) (PoM)

Nasal spray, mometasone furoate 50 micrograms/metered spray. Net price 140-spray unit = £7.68

Excipients include benzalkonium chloride, polysorbate 80

Dose**Prophylaxis and treatment of allergic rhinitis**

Child 6–12 years 50 micrograms (1 spray) into each nostril once daily

Child 12–18 years 100 micrograms (2 sprays) into each nostril once daily, increased if necessary to max. 200 micrograms (4 sprays) into each nostril once daily; when control achieved reduce to 50 micrograms (1 spray) into each nostril once daily

TRIAMCINOLONE ACETONIDE

Cautions see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 6 years

Indications and dose**Treatment of allergic rhinitis**

Child 2–6 years 55 micrograms (1 spray) into each nostril once daily; max. duration of treatment 3 months

Child 6–12 years 55 micrograms (1 spray) into each nostril once daily, increased if necessary to 110 micrograms (2 sprays) into each nostril once daily; when control achieved, reduce to 55 micrograms (1 spray) into each nostril once daily; max. duration of treatment 3 months

Child 12–18 years 110 micrograms (2 sprays) into each nostril once daily; when control achieved, reduce to 55 micrograms (1 spray) into each nostril once daily

Nasacort® (Sanofi-Aventis) (PoM)

Aqueous nasal spray, triamcinolone acetonide 55 micrograms/metered spray. Net price 120-spray unit = £7.39

Excipients include benzalkonium chloride, disodium edetate, polysorbate 80

Cromoglicate**SODIUM CROMOGLICATE**
(Sodium Cromoglycate)

Side-effects local irritation; rarely transient bronchospasm

Licensed use licensed for use in children (age range not specified by manufacturers)

Indications and dose

Prophylaxis of allergic rhinitis for dose, see under preparations

Rynacrom® (Sanofi-Aventis)

4% aqueous nasal spray, sodium cromoglicate 4% (5.2 mg/spray). Net price 22 mL (150-spray unit with pump) = £17.07

Excipients include benzalkonium chloride, disodium edetate

Dose

nose, 1 spray into each nostril 2–4 times daily

12.2.2 Topical nasal decongestants

Sodium chloride 0.9% given as nasal drops or spray may relieve nasal congestion by helping to liquefy mucous secretions in children with rhinitis. In infants, 1–2 drops of sodium chloride 0.9% solution in each nostril before feeds will help relieve congestion and allow more effective suckling.

Inhalation of **warm moist air** is useful in the treatment of symptoms of acute nasal congestion in infants and children, but the use of boiling water for steam inhalation is dangerous for children and should **not** be recommended. Volatile substances (section 3.8) such as menthol and eucalyptus may encourage inhalation of warm moist air.

Topical nasal decongestants containing sympathomimetics can cause rebound congestion (*rhinitis medicamentosa*) following prolonged use (more than 7 days), and are therefore of limited value in the treatment of nasal congestion.

Ephedrine nasal drops is the least likely of the sympathomimetic nasal decongestants to cause rebound congestion and can provide relief for several hours. The more potent sympathomimetic drugs **oxymetazoline** and **xylometazoline** are more likely to cause a rebound effect.

The CHM/MHRA has stated that non-prescription cough and cold medicines containing ephedrine, oxymetazoline, or xylometazoline can be considered for up to 5 days' treatment in children aged 6–12 years after basic principles of best care have been tried; these medicines should not be used in children under 6 years of age (section 3.9.1).

Non-allergic watery rhinorrhoea often responds well to treatment with the antimuscarinic **ipratropium bromide**.

Recurrent, persistent bleeding may respond to the use of a sympathomimetic nasal spray; if infection is present, chlorhexidine and neomycin (*Naseptin*®) cream (section 12.2.3) may be effective.

Systemic nasal decongestants—see section 3.10.

Sinusitis and oral pain Sinusitis affecting the maxillary antrum can cause pain in the upper jaw. Where this is associated with blockage of the opening from the sinus into the nasal cavity, it may be helpful to relieve the congestion with inhalation of warm moist air (section 3.8) or with **ephedrine nasal drops** (see above). For antibacterial treatment of sinusitis, see Table 1, section 5.1.

Sympathomimetics

EPHEDRINE HYDROCHLORIDE

Cautions see notes above; also avoid excessive or prolonged use; hyperthyroidism; diabetes mellitus; cardiovascular disease (including hypertension); interactions: Appendix 1 (sympathomimetics)

Pregnancy avoid

Breast-feeding avoid

Side-effects local irritation, nausea, headache; after excessive use tolerance with diminished effect, rebound congestion; cardiovascular effects also reported

Licensed use not licensed for use in children under 12 years

Indications and dose

Nasal congestion (see notes above)

Child 12–18 years instil 1–2 drops (0.5% strength) into each nostril up to 4 times daily when required; max. duration 7 days

¹Ephedrine (Non-proprietary)

Nasal drops, ephedrine hydrochloride 0.5%, net price 10 mL = £1.49; 1%, 10 mL = £1.54

Note The BP directs that if no strength is specified 0.5% drops should be supplied

Dental prescribing on NHS Ephedrine nasal drops may be prescribed

XYLOMETAZOLINE HYDROCHLORIDE

Cautions see under Ephedrine Hydrochloride and notes above; also angle-closure glaucoma; avoid excessive or prolonged use

Pregnancy avoid

Breast-feeding manufacturer advises caution—no information available

Side-effects see under Ephedrine Hydrochloride and notes above; also reported transient visual disturbances; in small children, also restlessness, sleep disturbances, and hallucinations (discontinue treatment)

Indications and dose

Nasal congestion for dose, see under preparations

Xylometazoline (Non-proprietary)

Nasal drops, xylometazoline hydrochloride 0.1%, net price 10 mL = £2.10

Dose

Child 12–18 years instil 2–3 drops into each nostril 2–3 times daily when required; max. duration 7 days

Brands include *Otradrops*®, *Otrivine*® JMS

Paediatric nasal drops, xylometazoline hydrochloride 0.05%, net price 10 mL = £1.91

Dose

Child 6–12 years instil 1–2 drops into each nostril 1–2 times daily when required; max. duration 5 days

Brands include *Otradrops*®, *Otrivine*® JMS

Nasal spray, xylometazoline hydrochloride 0.1%, net price 10 mL = £2.10

Dose

Child 12–18 years apply 1 spray into each nostril 1–3 times daily when required; max. duration 7 days

Brands include *Otrivine*® JMS, *Otrivine*® Allergy Relief

Antimuscarinic

IPRATROPIUM BROMIDE

Cautions see section 3.1.2; avoid spraying near eyes

Side-effects epistaxis, nasal dryness, and irritation; less frequently nausea, headache, and pharyngitis; very rarely antimuscarinic effects such as gastro-

1. Can be sold to the public provided no more than 180 mg of ephedrine base (or salts) are supplied at one time, and pseudoephedrine salts are not supplied at the same time; for conditions that apply to supplies made at the request of a patient, see *Medicines, Ethics and Practice*, London, Pharmaceutical Press (always consult latest edition)

intestinal motility disturbances, palpitations, and urinary retention

Indications and dose

Rhinorrhoea associated with allergic and non-allergic rhinitis

Child 12–18 years apply 42 micrograms (2 sprays) into each nostril 2–3 times daily

Asthma and reversible airways obstruction section 3.1.2


Rinatec® (Boehringer Ingelheim) (PoM)

Nasal spray 0.03% ipratropium bromide 21 micrograms/metered spray. Net price 180-dose unit = £6.54

Excipients include benzalkonium chloride, disodium edetate

12.2.3 Nasal preparations for infection

There is **no** evidence that topical anti-infective nasal preparations have any therapeutic value in rhinitis or sinusitis; for elimination of nasal staphylococci, see below. Acute complications such as periorbital cellulitis require hospital treatment. For systemic treatment of sinusitis, see Table 1, section 5.1.

Betnesol-N® (RPH) (PoM) 

Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%, neomycin sulfate 0.5%. Net price 10 mL = £2.39

Excipients include benzalkonium chloride, disodium edetate

Dose

nose, instil 2–3 drops into each nostril 2–3 times daily

Note *Betnesol-N®* licensed for use in children (age range not specified by manufacturer)

Nasal staphylococci

Elimination of organisms such as staphylococci from the nasal vestibule can be achieved by the use of a cream containing **chlorhexidine** and **neomycin** (*Naseptin®*), but re-colonisation frequently occurs. Coagulase-positive staphylococci are present in the noses of 40% of the population. A nasal ointment containing **mupirocin** is also available; it should probably be held in reserve for resistant infections. In hospitals or in care establishments, mupirocin nasal ointment should be reserved for the *eradication* (in both patients and staff) of nasal carriage of methicillin-resistant *Staphylococcus aureus* (MRSA). The ointment should be applied 3 times daily for 5 days and a sample taken 2 days after treatment to confirm eradication. The course may be repeated if the sample is positive (and the throat is not colonised). To avoid the development of resistance, the treatment course should not exceed 7 days and the course should not be repeated on more than one occasion. If the MRSA strain is mupirocin-resistant or does not respond after 2 courses, consider alternative products such as chlorhexidine and neomycin cream. For eradication of MRSA also consult local infection control policy. See section 13.10.1 for treatment of MRSA-infected open wounds. See section 5.1.1.2 for *treatment* of children with MRSA-positive throat swabs or systemic MRSA infection.

Bactroban Nasal® (GSK) (PoM)

Nasal ointment, mupirocin 2% (as calcium salt) in white soft paraffin basis. Net price 3 g = £3.54

Dose

For eradication of nasal carriage of staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA)

Apply 2–3 times daily to the inner surface of each nostril (see notes above)

Naseptin® (Alliance) (PoM)

Cream, chlorhexidine hydrochloride 0.1%, neomycin sulfate 0.5%, net price 15 g = £1.90

Excipients include arachis (peanut) oil, cetostearyl alcohol

Dose

For eradication of nasal carriage of staphylococci

Apply to nostrils 4 times daily for 10 days

For preventing nasal carriage of staphylococci

Apply to nostrils twice daily

12.3 Drugs acting on the oropharynx

12.3.1 Drugs for oral ulceration and inflammation

12.3.2 Oropharyngeal anti-infective drugs

12.3.3 Lozenges and sprays

12.3.4 Mouthwashes and gargles

12.3.5 Treatment of dry mouth

12.3.1 Drugs for oral ulceration and inflammation

Ulceration of the oral mucosa may be caused by trauma (physical or chemical), recurrent aphthous ulcers, infections, carcinoma, dermatological disorders, nutritional deficiencies, gastro-intestinal disease, haematopoietic disorders, and drug therapy. It is important to establish the diagnosis in each case as the majority of these lesions require specific management in addition to local treatment. Local treatment aims to protect the ulcerated area, to relieve pain, to reduce inflammation, or to control secondary infection. Children with an unexplained mouth ulcer of more than 3 weeks' duration require urgent referral to hospital to exclude secondary causes such as leukaemia.

Simple mouthwashes A **saline** mouthwash (section 12.3.4) may relieve the pain of traumatic ulceration. The mouthwash is made up with warm water and used at frequent intervals until the discomfort and swelling subsides.

Antiseptic mouthwashes Secondary bacterial infection may be a feature of any mucosal ulceration; it can increase discomfort and delay healing. Use of **chlorhexidine** mouthwash (section 12.3.4) is often beneficial and may accelerate healing of recurrent aphthous ulcers.

Corticosteroids Topical corticosteroid therapy may be used for some forms of oral ulceration; for aphthous ulcers it is most effective if applied in the 'prodromal' phase. Thrush or other types of candidiasis are recognised complications of corticosteroid treatment.

Hydrocortisone oromucosal tablets are useful in recurrent aphthous ulcers and erosive lichenoid lesions.

Beclometasone dipropionate inhaler (p. 146) 50–100 micrograms sprayed twice daily on the oral mucosa is used to manage oral ulceration [unlicensed indication]. Alternatively, **betamethasone** soluble tablets dissolved in water, can be used as a mouthwash to treat oral ulceration.

Systemic corticosteroid therapy (section 6.3.2) is reserved for severe conditions such as pemphigus vulgaris.

Local analgesics Local analgesics have a limited role in the management of oral ulceration. When applied topically their action is of a relatively short duration and analgesia cannot be maintained continuously throughout the day. When local anaesthetics are used in the mouth, care must be taken not to produce anaesthesia of the pharynx before meals as this might lead to choking.

Benzydamine and **Flurbiprofen** are non-steroidal anti-inflammatory drugs (NSAIDs). Benzydamine mouthwash or spray may be useful in reducing the discomfort associated with a variety of ulcerative conditions. It has also been found to be effective in reducing the discomfort of tonsillectomy and post-irradiation mucositis. Some children find the full-strength mouthwash causes some stinging and, for them, it should be diluted with an equal volume of water. Flurbiprofen lozenges are licensed for the relief of sore throat in adolescents.

Choline salicylate is a derivative of salicylic acid and has some analgesic action. The dental gel may provide relief for recurrent aphthous ulcers in children over 16 years of age.

Periodontitis Low-dose **doxycycline** (*Periostat*®) is licensed as an adjunct to scaling and root planing for the treatment of periodontitis in children over 12 years; a low dose of doxycycline reduces collagenase activity without inhibiting bacteria associated with periodontitis. For anti-infectives used in the treatment of destructive (refractory) forms of periodontal disease, see section 12.3.2 and Table 1, section 5.1. For mouthwashes used for oral hygiene and plaque inhibition, see section 12.3.4.

BENZYDAMINE HYDROCHLORIDE

Side-effects occasional numbness or stinging; rarely hypersensitivity reactions

Indications and dose

Painful inflammatory conditions of oropharynx

- As a mouthwash (benzydamine hydrochloride 0.15%)

Child 13–18 years rinse or gargle using 15 mL (dilute with an equal volume of water if stinging occurs) every 1½–3 hours as required, usually for not more than 7 days

- As an oromucosal spray (benzydamine hydrochloride 0.15%)

Child under 6 years 1 spray per 4 kg body-weight (max. 4 sprays) onto affected area every 1½–3 hours

Child 6–12 years 4 sprays onto affected area every 1½–3 hours

Child 12–18 years 4–8 sprays onto affected area every 1½–3 hours

Benzydamine hydrochloride (Non-proprietary)

Mouthwash, benzydamine hydrochloride 0.15%, net price 300 mL = £6.45

Brands include Ooze®

Oromucosal spray, benzydamine hydrochloride 0.15%, net price 30 mL = £4.24

Brands include Ooze®

Dental prescribing on NHS Benzydamine Oromucosal Spray 0.15% may be prescribed

Diffiam® (Meda)

Mouthwash (oral rinse), green, benzydamine hydrochloride 0.15%, net price 200 mL (*Diffiam*® Sore Throat Rinse) = £4.64; 300 mL = £6.50

Dental prescribing on NHS May be prescribed as Benzydamine Mouthwash 0.15%

Oromucosal spray, benzydamine hydrochloride 0.15%, net price 30-mL unit = £4.24

CORTICOSTEROIDS

Contra-indications untreated oral infection

Side-effects occasional exacerbation of local infection; thrush or other candidal infections

Licensed use **Hydrocortisone mucoadhesive buccal tablets** licensed for use in children (under 12 years—on medical advice only); **betamethasone soluble tablets** not licensed for use in oral ulceration

Indications and dose

Oral and perioral lesions for dose, see under preparations

Betamethasone (Non-proprietary) (POM)

Soluble tablets, betamethasone 500 micrograms (as sodium phosphate), net price 100-tab pack = £18.95. Label: 10, 13, counselling, administration Dose

Oral ulceration

Child 12–18 years 500 micrograms dissolved in 20 mL water and rinsed around the mouth 4 times daily; not to be swallowed

Dental prescribing on NHS Betamethasone Soluble Tablets 500 micrograms may be prescribed

Hydrocortisone (Non-proprietary)

Mucoadhesive buccal tablets (= oromucosal tablets), hydrocortisone 2.5 mg (as sodium succinate). Net price 20 = £4.24

Dose

1 lozenge 4 times daily, allowed to dissolve slowly in the mouth in contact with the ulcer

Dental prescribing on NHS May be prescribed as Hydrocortisone Oromucosal Tablets

DOXYCYCLINE

Cautions section 5.1.3; monitor for superficial fungal infection, particularly if predisposition to oral candidiasis

Contra-indications section 5.1.3

Hepatic impairment section 5.1.3

Renal impairment section 5.1.3

Pregnancy section 5.1.3

Breast-feeding section 5.1.3

Side-effects section 5.1.3; fungal superinfection

Indications and dose

See under preparations

Other indications section 5.1.3

Periostat® (Alliance) (PoM)

Tablets, f/c, doxycycline (as hyclate) 20 mg, net price 56-tab pack = £17.30. Label: 6, 11, 27, counselling, posture

Dose

Periodontitis (as an adjunct to gingival scaling and root planing)

Child 12–18 years 20 mg twice daily for 3 months

Counselling Tablets should be swallowed whole with plenty of fluid, while sitting or standing

Dental prescribing on NHS May be prescribed as Doxycycline Tablets 20 mg

Note May be difficult to obtain

Local application

For severe recurrent aphthous ulceration, a 100 mg doxycycline dispersible tablet can be stirred into a small amount of water then rinsed around the mouth for 2–3 minutes 4 times daily usually for 3 days; it should preferably not be swallowed [unlicensed indication].

Note Doxycycline stains teeth; avoid in children under 12 years of age

FLURBIPROFEN

Cautions section 10.1.1

Contra-indications section 10.1.1

Hepatic impairment section 10.1.1

Renal impairment section 10.1.1

Pregnancy section 10.1.1

Breast-feeding section 10.1.1

Side-effects taste disturbance, mouth ulcers (move lozenge around mouth; see also section 10.1.1)

Indications and dose

Relief of sore throat for dose, see under preparation

Strefen® (Reckitt Benckiser)

Lozenges, flurbiprofen 8.75 mg, net price 16 = £2.58

Dose

Child 12–18 years allow 1 lozenge to dissolve slowly in the mouth every 3–6 hours, max. 5 lozenges in 24 hours, for max. 3 days

SALICYLATES

Cautions frequent application, especially in children, may give rise to salicylate poisoning

Contra-indications children under 16 years

Reye's syndrome The CHM has advised that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reye's syndrome

Side-effects transient local burning sensation

Indications and dose

Mild oral and perioral lesions for dose, see under preparations

Choline salicylate

Choline Salicylate Dental Gel, BP

Oral gel, choline salicylate 8.7% in a flavoured gel basis, net price 15 g = £2.26

Brands include *Bonjela®* (sugar-free)

Dose

Child 16–18 years apply ½-inch of gel with gentle massage not more often than every 3 hours

Dental prescribing on NHS Choline Salicylate Dental Gel may be prescribed

Salicylic acid

Pyralvex® (Meda)

Oral paint, brown, rhubarb extract (anthraquinone glycosides 0.5%), salicylic acid 1%. Net price 10 mL with brush = £3.25

Excipients include ethanol

Dose

Child 16–18 years apply 3–4 times daily; max. duration 7 days

Note May cause temporary discolouration of teeth and oral mucosa

12.3.2 Oropharyngeal anti-infective drugs

Sore throat is usually a self-limiting condition often caused by viral infection which does not benefit from anti-infective treatment. Adequate analgesia may be all that is required. Systemic **antibacterials** (Table 1, section 5.1) should only be used in severe cases where there is concern for the child's overall clinical condition. Acute ulcerative gingivitis (Vincent's infection) requires treatment with oral **metronidazole** (section 5.1.11).

Benzydamine (section 12.3.1) may be beneficial in relieving pain and dysphagia in children, especially after tonsillectomy or the use of a nasogastric tube.

Oropharyngeal viral infections

Children with varicella-zoster infection often develop painful lesions in the mouth and throat. **Benzydamine** (section 12.3.1) may be used to provide local analgesia. **Chlorhexidine** mouthwash or gel (section 12.3.4) will control plaque accumulation if toothbrushing is painful and will also help to control secondary infection in general.

In severe herpetic stomatitis systemic **aciclovir** or **valaciclovir** (section 5.3.2.1) may be used for oral lesions associated with herpes zoster. Aciclovir and valaciclovir are also used to prevent frequently recurring herpes simplex lesions of the mouth particularly when associated with the initiation of erythema multiforme. For the treatment of labial herpes simplex infections, see section 13.10.3.

Oropharyngeal fungal infections

Fungal infections of the mouth are usually caused by *Candida* spp. (candidiasis or candidosis). Different types of oropharyngeal candidiasis are managed as follows:

Thrush Acute pseudomembranous candidiasis (thrush), is usually an acute infection but it may persist for months in patients receiving inhaled corticosteroids, cytotoxics, or broad-spectrum antibacterials. Thrush also occurs in patients with serious systemic disease associated with reduced immunity such as leukaemia, other malignancies, and HIV infection. Any predisposing condition should be managed appropriately. When thrush is associated with corticosteroid inhalers, rinsing the mouth with water (or cleaning a child's teeth) immediately after using the inhaler may avoid the problem. Treatment with **nystatin** or **miconazole** may be needed. **Fluconazole** (section 5.2.1) is effective for unresponsive infections or if a topical antifungal drug cannot be used. Topical therapy may not be adequate in immunocompromised children and an oral triazole antifungal is preferred (section 5.2.1).

Acute erythematous candidiasis Acute erythematous (atrophic) candidiasis is a relatively uncommon condition associated with corticosteroid and broad-spectrum antibacterial use and with HIV disease. It is usually treated with **fluconazole** (section 5.2.1).

Angular cheilitis Angular cheilitis (angular stomatitis) is characterised by soreness, erythema and fissuring at the angles of the mouth. It may represent a nutritional deficiency or it may be related to orofacial granulomatosis or HIV infection. Both yeasts (*Candida* spp.) and bacteria (*Staphylococcus aureus* and beta-haemolytic streptococci) are commonly involved as interacting, infective factors. While the underlying cause is being identified and treated, it is often helpful to apply **miconazole** cream (p. 594) or **sodium fusidate** ointment (p. 593); if the angular cheilitis is unresponsive to treatment, **miconazole** and **hydrocortisone** cream or ointment (p. 565) can be used.

Immunocompromised patients For advice on prevention of fungal infections in immunocompromised children see p. 305.

For the role of antiseptic mouthwashes in the prevention of oral candidiasis in immunocompromised children, see section 12.3.4.

Drugs used in oropharyngeal candidiasis **Nystatin** is not absorbed from the gastro-intestinal tract and is applied locally (as a suspension) to the mouth for treating local fungal infections. **Miconazole** is used by local application (as an oral gel) in the mouth but it is also absorbed to the extent that potential interactions need to be considered. **Miconazole** also has some activity against Gram-positive bacteria including streptococci and staphylococci. In neonates, **nystatin** oral suspension or **miconazole** oral gel is used for the treatment of oropharyngeal candidiasis; to prevent re-infection it is important to ensure that the mother's breast nipples and the teats of feeding bottles are cleaned adequately.

Fluconazole (section 5.2.1) given by mouth is reliably absorbed; it is used for infections that do not respond to topical therapy or when topical therapy cannot be used. **Itraconazole** (section 5.2.1) can be used for fluconazole-resistant infections.

If candidal infection fails to respond after 1 to 2 weeks of treatment with antifungal drugs the child should be sent for investigation to eliminate the possibility of underlying disease. Persistent infection may also be caused by re-infection from the genito-urinary or gastro-intestinal tract.

MICONAZOLE

Cautions avoid in acute porphyria (section 9.8.2); interactions: Appendix 1 (antifungals, imidazole)

Contra-indications impaired swallowing reflex in infants

Hepatic impairment avoid

Pregnancy manufacturer advises avoid if possible—toxicity at high doses in animal studies

Breast-feeding manufacturer advises caution—no information available

Side-effects nausea and vomiting, very rarely diarrhoea (usually on long-term treatment), hepatitis, rash, toxic epidermal necrolysis, and Stevens-Johnson syndrome

Licensed use not licensed for use in children under 4 months of age or during first 5–6 months of life of an infant born pre-term

Indications and dose

Prevention and treatment of oral candidiasis

• By mouth

Neonate 1 mL 2–4 times daily smeared around the inside of the mouth after feeds

Child 1 month–2 years 1.25 mL 4 times daily smeared around the inside of the mouth after meals

Child 2–18 years 2.5 mL 4 times daily after meals; retain near lesions before swallowing (orthodontic appliances should be removed at night and brushed with gel)

Prevention and treatment of intestinal candidiasis

• By mouth

Child 4 months–18 years 5 mg/kg 4 times daily; max. 250 mg (10 mL) 4 times daily

Note Treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared

¹Daktarin® (Janssen) (PoM)

Oral gel, sugar-free, orange-flavoured, **miconazole** 24 mg/mL (20 mg/g). Net price 15-g tube = £2.97, 80-g tube = £4.38. Label: 9, counselling, hold in mouth, after food

Excipients include ethanol

Dental prescribing on NHS May be prescribed as **Miconazole Oromucosal Gel**

NYSTATIN

Side-effects oral irritation and sensitisation, nausea reported

Licensed use suspension not licensed for use in neonates for the treatment of candidiasis

Indications and dose

Oral and perioral fungal infections

Neonate 100 000 units 4 times daily after feeds

Child 1 month–18 years 100 000 units 4 times daily after food

Note Treatment is usually given for 7 days, and continued for 48 hours after lesions have healed.

Skin infections section 13.10.2

Nystatin (Non-proprietary) (PoM)

Oral suspension, **nystatin** 100 000 units/mL, net price 30 mL = £20.46. Label: 9, counselling, use of pipette, hold in mouth, after food

Dental prescribing on NHS Nystatin Oral Suspension may be prescribed

Nystan® (Squibb) (PoM)

Oral suspension, yellow, **nystatin** 100 000 units/mL. Net price 30 mL with pipette = £1.91. Label: 9, counselling, use of pipette, hold in mouth, after food

Excipients include ethanol

12.3.3 Lozenges and sprays

There is no convincing evidence that antiseptic lozenges and sprays have a beneficial action and they sometimes irritate and cause sore tongue and sore lips. Some preparations also contain local anaesthetics which relieve pain but may cause sensitisation.

1. 15-g tube can be sold to the public

12.3.4 Mouthwashes and gargles

Superficial infections of the mouth are often helped by warm mouthwashes which have a mechanical cleansing effect and cause some local hyperaemia. However, to be effective, they must be used frequently and vigorously. Mouthwashes may not be suitable for children under 7 years (risk of the solution being swallowed); the mouthwash or dental gel may be applied using a cotton bud.

A warm saline mouthwash is ideal for its cleansing effect and can be prepared either by dissolving half a teaspoonful of salt in a glassful of warm water or by diluting **compound sodium chloride mouthwash** with an equal volume of warm water.

Mouthwashes containing an oxidising agent, such as **hydrogen peroxide**, may be useful in the treatment of acute ulcerative gingivitis (Vincent's infection). Hydrogen peroxide solution has also a mechanical cleansing effect arising from frothing when in contact with oral debris, but in concentrations greater than 1.5% may cause ulceration and tissue damage.

Chlorhexidine is an effective antiseptic which has the advantage of inhibiting plaque formation on the teeth. It does not, however, completely control plaque deposition and is not a substitute for effective toothbrushing. Moreover, chlorhexidine preparations do not penetrate significantly into stagnation areas and are therefore of little value in the control of dental caries or of periodontal disease once pocketing has developed. Chlorhexidine preparations are of little value in the control of acute necrotising ulcerative gingivitis. With prolonged use, chlorhexidine causes reversible brown staining of teeth and tongue. Chlorhexidine may be incompatible with some ingredients in toothpaste, causing an unpleasant taste in the mouth; rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing products.

Chlorhexidine can be used as a mouthwash, spray or gel for secondary infection in mucosal ulceration and for controlling gingivitis, as an adjunct to other oral hygiene measures. These preparations may also be used instead of toothbrushing where there is a painful periodontal condition (e.g. primary herpetic stomatitis) or if the child has a haemorrhagic disorder, or is disabled. Chlorhexidine mouthwash is used in the prevention of oral candidiasis in immunocompromised patients. Chlorhexidine mouthwash reduces the incidence of alveolar osteitis following tooth extraction. Chlorhexidine mouthwash should not be used for the prevention of endocarditis in children undergoing dental procedures.

CHLORHEXIDINE GLUCONATE

Side-effects mucosal irritation (if desquamation occurs, discontinue treatment or dilute mouthwash with an equal volume of water); taste disturbance; reversible brown staining of teeth, and of silicate or composite restorations; tongue discoloration; parotid gland swelling and hypersensitivity (including anaphylaxis) reported

Note Chlorhexidine gluconate may be incompatible with some ingredients in toothpaste; rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing product

Licensed use licensed for use in children (age range not specified by manufacturer); *Corsodyl*® not

licensed for use in children under 12 years (unless on the advice of a healthcare professional)

Indications and dose

See under preparations below

Chlorhexidine (Non-proprietary)

Mouthwash, chlorhexidine gluconate 0.2%, net price 300 mL = £3.45

Dose

Oral hygiene and plaque inhibition, oral candidiasis, gingivitis, and management of aphthous ulcers

Rinse mouth with 10 mL for about 1 minute twice daily

Corsodyl® (GSK Consumer Healthcare)

Dental gel, chlorhexidine gluconate 1%. Net price 50 g = £1.21

Dose

Oral hygiene and plaque inhibition and gingivitis

Brush on the teeth once or twice daily

Oral candidiasis and management of aphthous ulcers

Apply to affected areas once or twice daily

Dental prescribing on NHS May be prescribed as Chlorhexidine Gluconate Gel

Mouthwash, chlorhexidine gluconate 0.2%, net price 300 mL (original or mint) = £2.28, 600 mL (mint) = £3.85; alcohol-free, 300 mL (mint) = £2.73

Dose

Oral hygiene and plaque inhibition, oral candidiasis, gingivitis, and management of aphthous ulcers

Rinse mouth with 10 mL for about 1 minute twice daily

Dental prescribing on NHS May be prescribed as Chlorhexidine Mouthwash

Oral spray, chlorhexidine gluconate 0.2% (mint-flavoured). Net price 60 mL = £4.10

Dose

Oral hygiene and plaque inhibition, oral candidiasis, gingivitis, and management of aphthous ulcers

Apply as required to tooth, gingival, or ulcer surfaces using up to 12 actuations (approx. 0.14 mL/actuation) twice daily

Dental prescribing on NHS May be prescribed as Chlorhexidine Oral Spray

With chlorobutanol

Eludril® (Fabre)

Mouthwash or gargle, chlorhexidine gluconate 0.1%, chlorobutanol 0.5% (mint-flavoured), net price 90 mL = £1.36, 250 mL = £2.83, 500 mL = £5.06

Dose

Oral hygiene and plaque inhibition

Child 6–18 years use 10–15 mL (diluted with lukewarm water in measuring cup provided) 2–3 times daily

HEXETIDINE

Side-effects local irritation; *very rarely* taste disturbance and transient anaesthesia

Indications and dose

Oral hygiene for dose, see preparation below

Oraldene® (McNeil)

Mouthwash or gargle, red or blue-green (mint-flavoured), hexetidine 0.1%. Net price 100 mL = £1.43; 200 mL = £2.21

Dose

Child 6–18 years use 15 mL (undiluted) 2–3 times daily

HYDROGEN PEROXIDE

Side-effects hypertrophy of papillae of tongue on prolonged use

Indications and dose

Oral hygiene (see notes above); for dose, see under preparations

Hydrogen Peroxide Mouthwash, BP

Mouthwash, consists of Hydrogen Peroxide Solution 6% (= approx. 20 volume) BP

Dose

Rinse the mouth for 2–3 minutes with 15 mL diluted in half a tumblerful of warm water 2–3 times daily (see notes above)

Dental prescribing on NHS Hydrogen Peroxide Mouthwash may be prescribed

Peroxyl® (Colgate-Palmolive)

Mouthwash, hydrogen peroxide 1.5%, net price 300 mL = £2.94

Dose

Child 6–18 years, rinse the mouth with 10 mL for about 1 minute 3 times daily (after meals and at bedtime) for max. 7 days

SODIUM CHLORIDE

Indications and dose

Oral hygiene (see notes above); for dose, see under preparation

Sodium Chloride Mouthwash, Compound, BP

Mouthwash, sodium bicarbonate 1%, sodium chloride 1.5% in a suitable vehicle with a peppermint flavour

Dose

Extemporaneous preparations should be prepared according to the following formula: sodium chloride 1.5 g, sodium bicarbonate 1 g, concentrated peppermint emulsion 2.5 mL, double-strength chloroform water 50 mL, water to 100 mL

To be diluted with an equal volume of warm water

Dental prescribing on NHS Compound Sodium Chloride Mouthwash may be prescribed

12.3.5 Treatment of dry mouth

Dry mouth (xerostomia) may be caused by drugs with antimuscarinic (anticholinergic) side-effects (e.g. antispasmodics and sedating antihistamines), by irradiation of the head and neck region or by damage to or disease of the salivary glands. Children with a persistently dry mouth may develop a burning or scalded sensation and have poor oral hygiene; they may develop dental caries, periodontal disease, and oral infections (particularly candidiasis). Dry mouth may be relieved in many patients by simple measures such as frequent sips of cool drinks or sucking pieces of ice or sugar-free fruit pastilles. Sugar-free chewing gum stimulates salivation in patients with residual salivary function.

Artificial saliva can provide useful relief of dry mouth. A properly balanced artificial saliva should be of a neutral pH and contain electrolytes (including fluoride) to correspond approximately to the composition of saliva. The acidic pH of some artificial saliva products may be inappropriate.

Local treatment

Artificial saliva products with **ACBS approval** may be prescribed for children with dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome. SST tablets may also be prescribed on the NHS.

AS Saliva Orthana® (AS Pharma)

Oral spray, gastric mucin (porcine) 3.5%, xylitol 2%, sodium fluoride 4.2 mg/litre, with preservatives and flavouring agents, pH neutral, net price 50-mL bottle = £4.92; 500-mL refill = £34.27

Dose

(ACBS) spray 2–3 times onto oral and pharyngeal mucosa, when required

Dental prescribing on NHS *AS Saliva Orthana®* Oral Spray may be prescribed

Lozenges, mucin 65 mg, xylitol 59 mg, in a sorbitol basis, pH neutral, net price 30-lozenge pack = £3.50

Dose

(ACBS) allow 1 lozenge to dissolve slowly in the mouth when required

Note *AS Saliva Orthana®* lozenges do not contain fluoride

Dental prescribing on NHS *AS Saliva Orthana®* Lozenges may be prescribed

Biotène Oralbalance® (GSK)

Saliva replacement gel, lactoperoxidase, lactoferrin, lysozyme, glucose oxidase, xylitol in a gel basis, net price 50-g tube = £4.46

Dose

Symptomatic treatment of dry mouth

Apply to gums and tongue as required

Note Avoid use with toothpastes containing detergents (including foaming agents)

Dental prescribing on NHS *Biotène Oralbalance®* Saliva Replacement Gel may be prescribed as Artificial Saliva Gel

BioXtra® (RIS Products)

Gel, lactoperoxidase, lactoferrin, lysozyme, whey colostrum, xylitol and other ingredients, net price 40-mL tube = £3.94, 50-mL spray = £3.94

Dose

(ACBS) apply to oral mucosa as required

Dental prescribing on NHS *BioXtra®* Gel may be prescribed

Glandosane® (Fresenius Kabi)

Aerosol spray, carmellose sodium 500 mg, sorbitol 1.5 g, potassium chloride 60 mg, sodium chloride 42.2 mg, magnesium chloride 2.6 mg, calcium chloride 7.3 mg, and dipotassium hydrogen phosphate 17.1 mg/50 g, pH 5.75, net price 50-mL unit (neutral, lemon or peppermint flavoured) = £5.38

Dose

(ACBS) spray onto oral and pharyngeal mucosa as required

Dental prescribing on NHS *Glandosane®* Aerosol Spray may be prescribed

Saliveze® (Wyvern)

Oral spray, carmellose sodium (sodium carboxymethylcellulose), calcium chloride, magnesium chloride, potassium chloride, sodium chloride, and dibasic sodium phosphate, pH neutral, net price 50-mL bottle (mint-flavoured) = £3.50

Dose

(ACBS) 1 spray onto oral mucosa as required

Dental prescribing on NHS *Saliveze®* Oral Spray may be prescribed

Salivix® (Galen)

Pastilles, sugar-free, reddish-amber, acacia, malic acid and other ingredients. Net price 50-pastille pack = £3.50

Dose**Symptomatic treatment of dry mouth**

Suck 1 pastille when required

Dental prescribing on NHS *Salivix®* Pastilles may be prescribed as Artificial Saliva Pastilles

SST (Medac)

Tablets, sugar-free, citric acid, malic acid and other ingredients in a sorbitol base, net price 100-tab pack = £4.86

Dose**Symptomatic treatment of dry mouth in patients with impaired salivary gland function and patent salivary ducts**

Allow 1 tablet to dissolve slowly in the mouth when required

Dental prescribing on NHS May be prescribed as Saliva Stimulating Tablets

Xerotin® (SpePharm)

Oral spray, sugar-free, water, sorbitol, carmellose (carboxymethylcellulose), potassium chloride, sodium chloride, potassium phosphate, magnesium chloride, calcium chloride and other ingredients, pH neutral. Net price 100-mL unit = £6.86

Dose**Symptomatic treatment of dry mouth**

Spray as required

Dental prescribing on NHS *Xerotin®* Oral Spray may be prescribed as Artificial Saliva Oral Spray

13 Skin

13.1 Management of skin conditions	556
13.1.1 Vehicles	557
13.1.2 Suitable quantities for prescribing	557
13.1.3 Excipients and sensitisation	557
13.2 Emollient and barrier preparations	557
13.2.1 Emollients	558
13.2.1.1 Emollient bath and shower preparations	560
13.2.2 Barrier preparations	563
13.3 Topical antipruritics	563
13.4 Topical corticosteroids	564
13.5 Preparations for eczema and psoriasis	572
13.5.1 Preparations for eczema	572
13.5.2 Preparations for psoriasis	573
13.5.3 Drugs affecting the immune response	578
13.6 Acne and rosacea	580
13.6.1 Topical preparations for acne	581
13.6.2 Oral preparations for acne	584
13.7 Preparations for warts and caluses	586
13.8 Sunscreens and camouflagers	588
13.8.1 Sunscreen preparations	588
13.8.2 Camouflagers	589
13.9 Shampoos and other preparations for scalp conditions	590
13.10 Anti-infective skin preparations	591
13.10.1 Antibacterial preparations	591
13.10.1.1 Antibacterial preparations only used topically	592
13.10.1.2 Antibacterial preparations also used systemically	593
13.10.2 Antifungal preparations	594
13.10.3 Antiviral preparations	596
13.10.4 Parasitocidal preparations	597
13.10.5 Preparations for minor cuts and abrasions	599
13.11 Skin cleansers, antiseptics, and desloughing agents	599
13.11.1 Alcohols and saline	600

13.11.2 Chlorhexidine salts	600
13.11.3 Cationic surfactants and soaps	601
13.11.4 Iodine	601
13.11.5 Phenolics	601
13.11.6 Oxidisers and dyes	601
13.11.7 Desloughing agents	602
13.12 Antiperspirants	602
13.13 Topical circulatory preparations	602

This chapter also includes advice on the management of the following:

candidiasis, p. 594
 dermatophytoses, p. 594
 head lice, p. 597
 nappy rash, p. 563
 pityriasis versicolor, p. 594
 scabies, p. 597

For information on wound management products and elasticated garments, see BNF Appendix 5.

The British Association of Dermatologists' list of preferred unlicensed dermatological preparations (specials) is available at www.bad.org.uk.

13.1 Management of skin conditions

13.1.1 Vehicles	
13.1.2 Suitable quantities for prescribing	
13.1.3 Excipients and sensitisation	

When prescribing topical preparations for the treatment of skin conditions in children, the site of application, the condition being treated, and the child's (and carer's) preference for a particular vehicle all need to be taken into consideration.

Neonates Caution is required when prescribing topical preparations for neonates—their large body surface area in relation to body mass increases susceptibility to toxicity from systemic absorption of substances applied to the skin. Topical preparations containing potentially sensitising substances such as corticosteroids, aminoglycosides, iodine, and parasitocidal drugs should be avoided. Preparations containing alcohol should be avoided because they can dehydrate the skin, cause pain if applied to raw areas, and the alcohol can cause necrosis.

In *preterm neonates*, the skin is more fragile and offers a poor barrier, especially in the first fortnight after birth. Preterm infants, especially if below 32 weeks corrected gestational age, may also require special measures to maintain skin hydration.

13.1.1 Vehicles

The vehicle in topical preparations for the skin affects the degree of hydration, has a mild anti-inflammatory effect, and aids the penetration of the active drug. Therefore, the vehicle, as well as the active drug, should be chosen on the basis of their suitability for the child's skin condition.

Applications are usually viscous solutions, emulsions, or suspensions for application to the skin (including the scalp) or nails.

Collodions are painted on the skin and allowed to dry to leave a flexible film over the site of application.

Creams are emulsions of oil and water and are generally well absorbed into the skin. They may contain an antimicrobial preservative unless the active ingredient or basis is intrinsically bactericidal and fungicidal. Generally, creams are cosmetically more acceptable than ointments because they are less greasy and easier to apply.

Gels consist of active ingredients in suitable hydrophilic or hydrophobic bases; they generally have a high water content. Gels are particularly suitable for application to the face and scalp.

Lotions have a cooling effect and may be preferred to ointments or creams for application over a hairy area. Lotions in alcoholic basis can sting if used on broken skin. *Shake lotions* (such as calamine lotion) contain insoluble powders which leave a deposit on the skin surface.

Ointments are greasy preparations which are normally anhydrous and insoluble in water, and are more occlusive than creams. They are particularly suitable for chronic, dry lesions. The most commonly used ointment bases consist of soft paraffin or a combination of soft, liquid, and hard paraffin. Some ointment bases have both *hydrophilic* and *lipophilic* properties; they may have occlusive properties on the skin surface, encourage hydration, and also be miscible with water; they often have a mild anti-inflammatory effect. *Water-soluble ointments* contain macrogols which are freely soluble in water and are therefore readily washed off; they have a limited but useful role where ready removal is desirable.

Pastes are stiff preparations containing a high proportion of finely powdered solids such as zinc oxide and starch suspended in an ointment. They are used for circumscribed lesions such as those which occur in lichen simplex, chronic eczema, or psoriasis. They are less occlusive than ointments and can be used to protect inflamed, lichenified, or excoriated skin.

Dusting powders are used only rarely. They reduce friction between opposing skin surfaces. Dusting powders should not be applied to moist areas because they can cake and abrade the skin. Talc is a lubricant but it does not absorb moisture; it can cause respiratory irritation. Starch is less lubricant but absorbs water.

Dilution The BP directs that creams and ointments should **not** normally be diluted but that should dilution be necessary care should be taken, in particular, to prevent microbial contamination. The appropriate diluent should be used and heating should be avoided during mixing; excessive dilution may affect the stability of some creams. Diluted creams should normally be used within 2 weeks of their preparation.

13.1.2 Suitable quantities for prescribing

Suitable quantities of dermatological preparations to be prescribed for specific areas of the body

Area of the body	Creams and Ointments	Lotions
Face	15–30 g	100 mL
Both hands	25–50 g	200 mL
Scalp	50–100 g	200 mL
Both arms or both legs	100–200 g	200 mL
Trunk	400 g	500 mL
Groins and genitalia	15–25 g	100 mL

The amounts shown above are usually suitable for children 12–18 years for twice daily application for 1 week; smaller quantities will be required for children under 12 years. These recommendations **do not** apply to corticosteroid preparations.

13.1.3 Excipients and sensitisation

Excipients in topical products rarely cause problems. If a patch test indicates allergy to an excipient, then products containing the substance should be avoided (see also Anaphylaxis, p. 158). The following excipients in topical preparations are associated, rarely, with sensitisation; the presence of these excipients is indicated in the entries for topical products. See also Excipients, under General Guidance, p. 2.

Beeswax	Imidurea
Benzyl alcohol	Isopropyl palmitate
Butylated hydroxyanisole	N-(3-Chloroallyl)hexam-
Butylated hydroxytoluene	ium chloride (quater-
Cetostearyl alcohol	nium 15)
(including cetyl and	Polysorbates
stearyl alcohol)	Propylene glycol
Chlorocresol	Sodium metabisulfite
Edetic acid (EDTA)	Sorbic acid
Ethylenediamine	Wool fat and related sub-
Fragrances	stances including
Hydroxybenzoates (para-	lanolin ¹
bens)	

13.2 Emollient and barrier preparations

13.2.1 Emollients

13.2.2 Barrier preparations

Borderline substances The preparations marked 'ACBS' are regarded as drugs when prescribed in accordance with the advice of the Advisory Committee on Borderline Substances for the clinical conditions listed. Prescriptions issued in accordance with this advice and endorsed 'ACBS' will normally not be investigated. See Appendix 2 for listing by clinical condition.

1. Purified versions of wool fat have reduced the problem

13.2.1 Emollients

13.2.1.1 Emollient bath and shower preparations

Emollients hydrate the skin, soften the skin, act as barrier to water and external irritants, and are indicated for all dry or scaling disorders. Their effects are short-lived and they should be applied frequently even after improvement occurs. They are useful in dry and eczematous disorders, and to a lesser extent in psoriasis (section 13.5.2); they should be applied immediately after washing or bathing to maximise the effect of skin hydration. The choice of an appropriate emollient will depend on the severity of the condition, the child's (or carer's) preference, and the site of application. Emollient preparations contained within tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis. Ointments may exacerbate acne and folliculitis. Some ingredients rarely cause sensitisation (section 13.1.3) and this should be suspected if an eczematous reaction occurs. The use of aqueous cream as a leave-on emollient may increase the risk of skin reactions, particularly in eczema.

Fire hazard with paraffin-based emollients

Emulsifying ointment or 50% Liquid Paraffin and 50% White Soft Paraffin Ointment in contact with dressings and clothing is easily ignited by a naked flame. The risk is greater when these preparations are applied to large areas of the body, and clothing or dressings become soaked with the ointment. Children and their carers should be told to keep away from fire or flames and not to smoke when using these preparations. The risk of fire should be considered when using large quantities of any paraffin-based emollient.

Preparations such as **aqueous cream** (section 13.2.1.1) and **emulsifying ointment** can be used as soap substitutes; the preparation is rubbed on the skin before rinsing off completely. The addition of a bath oil (section 13.2.1.1) may also be helpful.

In the *neonate*, a preservative-free paraffin-based emollient hydrates the skin without affecting the normal skin flora; substances such as olive oil are also used. The development of blisters (epidermolysis bullosa) or ichthyosis may be alleviated by applying liquid and white soft paraffin ointment while awaiting dermatological investigation.

Preparations containing an antibacterial (section 13.10.1) should be avoided unless infection is present or is a frequent complication of the dry skin condition.

Urea is a keratin softener and hydrating agent used in the treatment of dry, scaling conditions (including ichthyosis). It is occasionally used with other topical agents such as corticosteroids to enhance penetration of the skin.

Non-proprietary emollient preparations

Emulsifying Ointment, BP

Ointment, emulsifying wax 30%, white soft paraffin 50%, liquid paraffin 20%, net price 500 g = £2.12

Excipients include cetostearyl alcohol

Hydrous Ointment, BP

Ointment, (oily cream), dried magnesium sulfate 0.5%, phenoxylethanol 1%, wool alcohols ointment 50%, in freshly boiled and cooled purified water, net price 500 g = £4.89

Liquid and White Soft Paraffin Ointment, NPF

Ointment, liquid paraffin 50%, white soft paraffin 50%, net price 500 g = £2.21

Paraffin, White Soft, BP

White petroleum jelly, net price 100 g = 51p

Paraffin, Yellow Soft, BP

Yellow petroleum jelly, net price 100 g = 49p

Proprietary emollient preparations

Aquamax[®] (Dermato Logical)

Cream, light liquid paraffin 8%, white soft paraffin 20%, phenoxylethanol 1%, net price 100 g = £1.89, 500 g = £3.99

Excipients include cetostearyl alcohol, polysorbate 60

Aquamol[®] (Thornton & Ross)

Cream, containing liquid paraffin, white soft paraffin, net price 50 g = £1.22, 500-g pump pack = £6.40

Excipients include cetostearyl alcohol, chlorocresol

Aveno[®] (J&J)

Cream, colloidal oatmeal in emollient basis, net price 100 mL = £3.97, 300-mL pump pack = £6.80

Excipients include benzyl alcohol, cetyl alcohol, isopropyl palmitate

ACBS: For endogenous and exogenous eczema, xeroderma, and ichthyosis

Lotion, colloidal oatmeal in emollient basis, net price 500 mL = £6.66

Excipients include benzyl alcohol, cetyl alcohol, isopropyl palmitate, stearyl alcohol

ACBS: as for *Aveno[®] Cream*

Cetraben[®] (Genus)

Emollient cream, white soft paraffin 13.2%, light liquid paraffin 10.5%, net price 50-g pump pack = £1.40, 150-g pump pack = £3.98, 500-g pump pack = £5.99, 1.05-kg pump pack = £11.62

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Dermamist[®] (Alliance)

Spray application, white soft paraffin 10% in a basis containing liquid paraffin, fractionated coconut oil, net price 250-mL pressurised aerosol unit = £5.97

Excipients none as listed in section 13.1.3

Note Flammable

Diprobase[®] (Schering-Plough)

Cream, cetomacrogol 2.25%, cetostearyl alcohol 7.2%, liquid paraffin 6%, white soft paraffin 15%, water-miscible basis used for *Diprosone[®]* cream, net price 50 g = £1.28; 500-g pump pack = £6.32

Excipients include cetostearyl alcohol, chlorocresol

Ointment, liquid paraffin 5%, white soft paraffin 95%, basis used for *Diprosone[®]* ointment, net price 50 g = £1.28, 500 g = £5.99

Excipients none as listed in section 13.1.3

Doublebase[®] (Dermal)

Gel, isopropyl myristate 15%, liquid paraffin 15%, net price 100 g = £2.65, 500 g = £5.83

Excipients none as listed in section 13.1.3

Dayleve Gel, isopropyl myristate 15%, liquid paraffin 15%, net price 100 g = £2.65, 500-g pump pack = £6.29

Excipients none as listed in section 13.1.3

E45® (Reckitt Benckiser)

Cream, light liquid paraffin 12.6%, white soft paraffin 14.5%, hypoallergenic anhydrous wool fat (hypoallergenic lanolin) 1% in self-emulsifying monostearin, net price 50 g = £1.61, 125 g = £2.90, 350 g = £5.17, 500-g pump pack = £5.62

Excipients include cetyl alcohol, hydroxybenzoates (parabens)

Lotion, light liquid paraffin 4%, cetomacrogol, white soft paraffin 10%, hypoallergenic anhydrous wool fat (hypoallergenic lanolin) 1% in glyceryl monostearate, net price 200 mL = £2.40, 500-mL pump pack = £4.50

Excipients include isopropyl palmitate, hydroxybenzoates (parabens), benzyl alcohol

ACBS: for symptomatic relief of dry skin conditions, such as those associated with atopic eczema and contact dermatitis

Emollin® (C D Medical)

Spray, liquid paraffin 50%, white soft paraffin 50% in aerosol basis, net price 150 mL = £3.97, 240 mL = £6.35

Excipients none as listed in section 13.1.3

Epaderm® (Mölnlycke)

Cream, yellow soft paraffin 15%, liquid paraffin 10%, emulsifying wax 5%, net price 50-g pump pack = £1.70, 500-g pump pack = £6.95

Excipients include cetostearyl alcohol, chlorocresol

Ointment, emulsifying wax 30%, yellow soft paraffin 30%, liquid paraffin 40%, net price 125 g = £3.85, 500 g = £6.53, 1 kg = £12.02

Excipients include cetostearyl alcohol

Hydromol® (Alliance)

Cream, sodium pidolate 2.5%, liquid paraffin 13.8%, net price 50 g = £2.19, 100 g = £4.09, 500 g = £11.92

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Ointment, yellow soft paraffin 30%, emulsifying wax 30%, liquid paraffin 40%, net price 125 g = £2.84, 500 g = £4.82, 1 kg = £8.96

Excipients include cetostearyl alcohol

Lipobase® (Astellas)

Cream, fatty cream basis used for *Locoid Lipocream®*, net price 50 g = £1.46

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

For dry skin conditions, also for use during treatment with topical corticosteroid and as diluent for *Locoid Lipocream®*

Oilatum® (Stiefel)

Cream, light liquid paraffin 6%, white soft paraffin 15%, net price 50 g = £1.63, 150 g = £2.46, 500-mL pump pack = £4.99, 1.05-litre pump pack = £9.98

Excipients include benzyl alcohol, cetostearyl alcohol

Oilatum® Junior Cream, light liquid paraffin 6%, white soft paraffin 15%, net price 150 g = £3.38, 350-mL pump pack = £4.65, 500-mL pump pack = £4.99, 1.05-litre pump pack = £9.98

Excipients include benzyl alcohol, cetostearyl alcohol

QV® (Sound Opinion)

Cream, glycerol 10%, light liquid paraffin 10%, white soft paraffin 5%, net price 100 g = £2.04, 500 g = £5.86, 1.05-kg pump pack = £11.94

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Intensive ointment, light liquid paraffin 50.5%, white soft paraffin 20%, net price 450 g = £5.65

Excipients include cetostearyl alcohol

Lotion, white soft paraffin 5%, net price 250 mL = £3.14, 500-mL pump pack = £5.24

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Ultrabase® (Derma UK)

Cream, water-miscible, containing liquid paraffin and white soft paraffin, net price 50 g = £1.40, 500-g pump pack = £4.80

Excipients include fragrance, hydroxybenzoates (parabens), disodium edetate, stearyl alcohol

Unguentum M® (Almirall)

Cream, containing saturated neutral oil, liquid paraffin, white soft paraffin, net price 50 g = £1.41, 100 g = £2.78, 200-mL pump pack = £5.50, 500 g = £8.48

Excipients include cetostearyl alcohol, polysorbate 40, propylene glycol, sorbic acid

ZeroAQs® (Thornton & Ross)

Cream, macrogol cetostearyl ether 1.8%, liquid paraffin 6%, white soft paraffin 15%, net price 100 g = £1.65, 500 g = £3.29

Excipients include cetostearyl alcohol, chlorocresol

Zerobase® (Thornton & Ross)

Cream, liquid paraffin 11%, net price 50 g = £1.04, 500-g pump pack = £5.26

Excipients include cetostearyl alcohol, chlorocresol

Zerocream® (Thornton & Ross)

Cream, liquid paraffin 12.6%, white soft paraffin 14.5%, net price 50 g = £1.17, 500-g pump pack = £4.08

Excipients include cetyl alcohol, hydroxybenzoates (parabens), lanolin anhydrous

Zeroguent® (Thornton & Ross)

Cream, light liquid paraffin 8%, white soft paraffin 4%, refined soya bean oil 5%, net price 100 g = £2.33, 500 g = £6.99

Excipients include cetostearyl alcohol, polysorbate 40, propylene glycol, sorbic acid

▲ **Preparations containing urea****Aquadrate®** (Alliance)

Cream, urea 10%, net price 100 g = £4.37

Excipients none as listed in section 13.1.3

Dose

Apply thinly twice daily

Balneum® (Almirall)

Cream, urea 5%, ceramide 0.1%, net price 50-g pump pack = £2.85, 500-g pump pack = £9.97

Excipients include cetostearyl alcohol, polysorbates, propylene glycol

Dose

Apply twice daily

Balneum® Plus Cream, urea 5%, laurmacrogols 3%, net price 100 g = £3.29, 500-g pump pack = £14.99

Excipients include benzyl alcohol, polysorbates

Dose

Apply twice daily

Calmurid® (Galderma)

Cream, urea 10%, lactic acid 5%, net price 100 g = £9.27, 500-g pump pack = £35.70

Excipients none as listed in section 13.1.3

Dose

Apply a thick layer for 3–5 minutes, massage into area, and remove excess, usually twice daily. Use half-strength cream for 1 week if stinging occurs

Note Can be diluted with aqueous cream (life of diluted cream 14 days)

Dermatonic Once Heel Balm® (Dermatonic)

Cream, urea 25%, net price 75 mL = £3.60, 200 mL = £8.50

Excipients include beeswax, lanolin

Dose

Child 12–18 years apply once daily to dry skin on soles of feet

E45® Itch Relief Cream (Reckitt Benckiser)

Cream, urea 5%, macrogol lauryl ether 3%, net price 50 g = £2.81, 100 g = £3.74, 500-g pump pack = £14.99

Excipients include benzyl alcohol, polysorbates

Dose

Apply twice daily

Eucerin® Intensive (Beiersdorf)

Cream, urea 10%, net price 100 mL = £7.59

Excipients include benzyl alcohol, isopropyl palmitate, wool fat

Dose

Apply thinly and rub into area twice daily

Lotion, urea 10%, net price 250 mL = £7.93

Excipients include benzyl alcohol, isopropyl palmitate

Dose

Apply sparingly and rub into area twice daily

Flexitol® (LaCorium)

Heel balm, urea 25%, net price 40 g = £2.75, 75 g = £3.80, 200 g = £9.40, 500 g = £14.75

Excipients include benzyl alcohol, cetostearyl alcohol, fragrance, lanolin

Dose

Child 12–18 years apply 1–2 times daily to dry skin on soles of feet and heels

Hydromol® Intensive (Alliance)

Cream, urea 10%, net price 30 g = £1.64, 100 g = £4.37

Excipients none as listed in section 13.1.3

Dose

Apply thinly twice daily

Nutraplus® (Galderma)

Cream, urea 10%, net price 100 g = £4.37

Excipients include hydroxybenzoates (parabens), propylene glycol

Dose

Apply 2–3 times daily

▲ **With antimicrobials****Dermol®** (Dermal)

Cream, benzalkonium chloride 0.1%, chlorhexidine hydrochloride 0.1%, isopropyl myristate 10%, liquid paraffin 10%, net price 100-g tube = £2.86, 500-g pump pack = £6.63

Excipients include cetostearyl alcohol

Dose

Apply to skin or use as soap substitute

Dermol® 500 Lotion, benzalkonium chloride 0.1%, chlorhexidine hydrochloride 0.1%, liquid paraffin 2.5%, isopropyl myristate 2.5%, net price 500-mL pump pack = £6.04

Excipients include cetostearyl alcohol

Dose

Apply to skin or use as soap substitute

Eczmol® (Genus)

Cream, chlorhexidine gluconate 1% in emollient basis, net price 250 mL = £3.70

Excipients include cetostearyl alcohol

Dose

Apply to skin or use as soap substitute

13.2.1.1 **Emollient bath and shower preparations**

Emollient bath additives should be added to bath water; some can be applied to wet skin undiluted and rinsed off. Hydration can be improved by soaking in the bath for 10–20 minutes. In dry skin conditions soap should be avoided (see section 13.2.1 for soap substitutes).

The quantities of bath additives recommended for older children are suitable for an adult-size bath. Proportionately less should be used for a child-size bath or a washbasin; recommended bath additive quantities for younger children reflect this.

These preparations make skin and surfaces slippery—particular care is needed when bathing a child.

Aqueous Cream, BP

Cream, emulsifying ointment 30%, ¹phenoxyethanol 1% in freshly boiled and cooled purified water, net price 100 g = 90p, 500 g = £4.50

Excipients include cetostearyl alcohol

1. The BP permits use of alternative antimicrobials provided their identity and concentration are stated on the label

Aquamax® (Dermato Logical)

Cream wash, light liquid paraffin 8%, white soft paraffin 20%, phenoxyethanol 1%, net price 250 g = £2.99

Excipients include cetostearyl alcohol, polysorbate 60
Dose

Apply to wet or dry skin and rinse

Aveeno® (J&J)

Bath oil, colloidal oatmeal, white oat fraction in emollient basis, net price 250 mL = £4.49

Excipients include beeswax, fragrance

ACBS: for endogenous and exogenous eczema, xeroderma, and ichthyosis

Dose

Child 2–18 years add 20–30 mL to bath water or apply to wet skin and rinse

Balneum® (Almirall)

Balneum® bath oil, soya oil 84.75%, net price 200 mL = £2.48, 500 mL = £5.38, 1 litre = £10.39

Excipients include butylated hydroxytoluene, propylene glycol, fragrance

Dose

Neonate add 5–15 mL to bath water; do not use undiluted

Child 1 month–2 years add 5–15 mL to bath water; do not use undiluted

Child 2–18 years add 20–60 mL to bath water; do not use undiluted

Balneum Plus® bath oil, soya oil 82.95%, mixed laurumacrogols 15%, net price 500 mL = £6.66

Excipients include butylated hydroxytoluene, propylene glycol, fragrance

Dose

Neonate add 5 mL to bath water or apply to wet skin and rinse

Child 1 month–2 years add 5 mL to bath water or apply to wet skin and rinse

Child 2–18 years add 10–20 mL to bath water or apply to wet skin and rinse

Cetaben® (Genus)

Emollient bath additive, light liquid paraffin 82.8%, net price 500 mL = £5.75

Excipients none as listed in section 13.1.3

Dose

Neonate add ½ capful to bath water or apply to wet skin and rinse

Child 1 month–12 years add ½–1 capful to bath water or apply to wet skin and rinse

Child 12–18 years add 1–2 capfuls to bath water or apply to wet skin and rinse

Dermal® (Dermal)

Bath emollient, acetylated wool alcohols 5%, liquid paraffin 65%, net price 500 mL = £3.44

Excipients none as listed in section 13.1.3

Dose

Neonate add 5 mL to bath water or apply to wet skin and rinse

Child 1 month–12 years add 5–10 mL to bath water or apply to wet skin and rinse

Child 12–18 years add 15–20 mL to bath water or apply to wet skin and rinse

Doublebase® (Dermal)

Emollient bath additive, liquid paraffin 65%, net price 500 mL = £5.45

Excipients include cetostearyl alcohol

Dose

Neonate add 5–10 mL to bath water

Child 1 month–12 years add 5–10 mL to bath water

Child 12–18 years add 15–20 mL to bath water

Emollient shower gel, isopropyl myristate 15%, liquid paraffin 15%, net price 200 g = £5.21

Excipients none as listed in section 13.1.3

Note Also available as Doublebase® Emollient Wash Gel

Dose

Apply to wet or dry skin and rinse, or apply to dry skin after showering

E45® (Reckitt Benckiser)

Emollient bath oil, cetyl dimeticone 5%, liquid paraffin 91%, net price 250 mL = £3.19, 500 mL = £5.11

Excipients none as listed in section 13.1.3

ACBS: for endogenous and exogenous eczema, xeroderma, and ichthyosis

Dose

Neonate add 5 mL to bath water or apply to wet skin and rinse

Child 1 month–12 years add 5–10 mL to bath water or apply to wet skin and rinse

Child 12–18 years add 15 mL to bath water or apply to wet skin and rinse

Emollient wash cream, zinc oxide 5% in an emollient basis, net price 250-mL pump pack = £3.19

Excipients none as listed in section 13.1.3

ACBS: for endogenous and exogenous eczema, xeroderma, and ichthyosis

Dose

Use as a soap substitute

Hydromol® (Alliance)

Bath and Shower Emollient, isopropyl myristate 13%, light liquid paraffin 37.8%, net price 350 mL = £3.88, 500 mL = £4.42, 1 litre = £8.80

Excipients none as listed in section 13.1.3

Dose

Neonate add ½ capful to bath water or apply to wet skin and rinse

Child 1 month–12 years add ½–2 capfuls to bath water or apply to wet skin and rinse

Child 12–18 years add 1–3 capfuls to bath water or apply to wet skin and rinse

LPL 63.4® (Huxley)

Emollient bath additive, light liquid paraffin 63.4%, net price 500 mL = £3.10

Excipients include acetylated wool alcohols, isopropyl palmitate

Dose

Neonate add ½ capful to bath water or apply to wet skin and rinse

Child 1 month–12 years add ½–2 capfuls to bath water or apply to wet skin and rinse

Child 12–18 years add 1–3 capfuls to bath water or apply to wet skin and rinse

Oilatum® (Stiefel)

Emollient bath additive (emulsion), light liquid paraffin 63.4%, net price 250 mL = £2.75, 500 mL = £4.57

Excipients include acetylated lanolin alcohols, isopropyl palmitate, fragrance

Dose

Neonate add ½ capful to bath water or apply to wet skin and rinse

Child 1 month–12 years add ¼–2 capfuls to bath water or apply to wet skin and rinse

Child 12–18 years add 1–3 capfuls to bath water or apply to wet skin and rinse

Junior bath additive, light liquid paraffin 63.4%, net price 150 mL = £2.82, 250 mL = £3.25, 300 mL = £5.10, 600 mL = £5.89

Excipients include acetylated lanolin alcohols, isopropyl palmitate

Dose

Neonate add ½ capful to bath water or apply to wet skin and rinse

Child 1 month–12 years add ½–2 capfuls to bath water or apply to wet skin and rinse

Child 12–18 years add 1–3 capfuls to bath water or apply to wet skin and rinse

Shower emollient (gel), light liquid paraffin 70%, net price (with fragrance or fragrance-free) 150 g = £5.15

Excipients none as listed in section 13.1.3

Dose

Apply to wet skin and rinse

QV® (Sound Opinion)

Bath oil, light liquid paraffin 85.13%, net price 200 mL = £2.20, 500 mL = £4.66

Excipients none as listed in section 13.1.3

Dose

Neonate add 5 mL to bath water or apply to wet skin and rinse

Child 1 month–1 year add 5 mL to bath water or apply to wet skin and rinse

Child 1–18 years add 10 mL to bath water or apply to wet skin and rinse

Gentle wash, glycerol 15%, net price 250 mL = £3.14, 500-mL pump pack = £5.24

Excipients include hydroxybenzoates (parabens)

Dose

Use as a soap substitute

Zerolatum® (Thornton & Ross)

Emollient medicinal bath oil, liquid paraffin 65%, net price 500 mL = £4.79

Excipients include acetylated wool alcohols

Dose

Child 1 month–12 years add 5–10 mL to bath water

Child 12–18 years add 15–20 mL to bath water

Zeroneum® (Thornton & Ross)

Bath oil, refined soya bean oil 83.35%, net price 500 mL = £4.48

Excipients include butylated hydroxytoluene, fragrance, propylene glycol

Dose

Child 1 month–12 years add 5 mL to bath water

Child 12–18 years add 20 mL to bath water

With antimicrobials**Dermol®** (Dermal)

Dermol® 600 Bath Emollient, benzalkonium chloride 0.5%, liquid paraffin 25%, isopropyl myristate 25%, net price 600 mL = £7.55

Excipients include polysorbate 60

Dose

Child 1 month–2 years add 5–15 mL to bath water; do not use undiluted

Child 2–18 years add 15–30 mL to bath water; do not use undiluted

Dermol® 200 Shower Emollient, benzalkonium chloride 0.1%, chlorhexidine hydrochloride 0.1%, liquid paraffin 2.5%, isopropyl myristate 2.5%, net price 200 mL = £3.55

Excipients include cetostearyl alcohol

Dose

Apply to skin or use as soap substitute

Dermol® Wash Emulsion, benzalkonium chloride 0.1%, chlorhexidine hydrochloride 0.1%, liquid paraffin 2.5%, isopropyl myristate 2.5%, net price 200-mL pump pack = £3.55

Excipients include cetostearyl alcohol

Dose

Apply to skin or use as soap substitute

Emulsiderm® (Dermal)

Liquid emulsion, benzalkonium chloride 0.5%, liquid paraffin 25%, isopropyl myristate 25%, net price 300 mL (with 15-mL measure) = £3.85, 1 litre (with 30-mL measure) = £12.00

Excipients include polysorbate 60

Dose

Child 1 month–2 years add 5–10 mL to bath water or rub into dry skin until absorbed

Child 2–18 years add 10–30 mL to bath water or rub into dry skin until absorbed

Oilatum® Plus (Stiefel)

Bath additive, benzalkonium chloride 6%, triclosan 2%, light liquid paraffin 52.5%, net price 500 mL = £6.98

Excipients include acetylated lanolin alcohols, isopropyl palmitate

Dose

Child 6 months–1 year add 1 mL to bath water; do not use undiluted

Child 1–18 years add 1–2 capfuls to bath water; do not use undiluted

Zerolatum® Plus (Thornton & Ross)

Bath additive, benzalkonium chloride 6%, triclosan 2%, light liquid paraffin 51.66%, net price 500 mL = £5.82

Excipients include acetylated lanolin alcohols, isopropyl palmitate, polysorbate 80

Dose

Child 6 months–1 year add 1 mL to bath water; do not use undiluted

Child 1–18 years add 1–2 capfuls to bath water; do not use undiluted

With tar

Section 13.5.2

13.2.2 Barrier preparations

Barrier preparations often contain water-repellent substances such as **dimeticone**, natural oils, and paraffins, to help protect the skin from abrasion and irritation; they are used to protect intact skin around stomas and pressure sores, and as a barrier against nappy rash. In neonates, barrier preparations which do not contain potentially sensitising excipients (section 13.1.3) are preferred. Where the skin has broken down, barrier preparations have a limited role in protecting adjacent skin. Barrier preparations with zinc oxide or titanium salts are used to aid healing of uninfected, excoriated skin.

Nappy rash (Dermatitis) The first line of treatment is to ensure that nappies are changed frequently and that tightly fitting water-proof pants are avoided. The rash may clear when left exposed to the air and a barrier preparation, applied with each nappy change, can be helpful. A mild corticosteroid such as hydrocortisone 0.5% or 1% (section 13.4) can be used if inflammation is causing discomfort, but it should be avoided in neonates. The barrier preparation should be applied after the corticosteroid preparation to prevent further damage. Preparations containing hydrocortisone should be applied for no more than a week; the hydrocortisone should be discontinued as soon as the inflammation subsides. The occlusive effect of nappies and water-proof pants may increase absorption of corticosteroids (for cautions, see section 13.4). If the rash is associated with candidal infection, a topical antifungal such as clotrimazole cream (section 13.10.2) can be used. Topical antibacterial preparations (section 13.10.1) can be used if bacterial infection is present; treatment with an oral antibacterial may occasionally be required in severe or recurrent infection. Hydrocortisone may be used in combination with antimicrobial preparations if there is considerable inflammation, erosion, and infection.

■ Non-proprietary barrier preparations

Zinc and Castor Oil Ointment, BP

Ointment, zinc oxide 7.5%, castor oil 50%, arachis (peanut) oil 30.5%, white beeswax 10%, cetostearyl alcohol 2%, net price 500 g = £6.41

■ Proprietary barrier preparations

Conotrane® (Astellas)

Cream, benzalkonium chloride 0.1%, dimeticone 22%, net price 100 g = 88p, 500 g = £3.51

Excipients include cetostearyl alcohol, fragrance

Drapolene® (Omega Pharma)

Cream, benzalkonium chloride 0.01%, cetrimide 0.2% in a basis containing white soft paraffin, cetyl alcohol and wool fat, net price 100 g = £1.76, 200 g = £2.86, 350 g = £4.28

Excipients include cetyl alcohol, chlorocresol, wool fat

Medicaid® (LPC)

Cream, cetrimide 0.5% in a basis containing light liquid paraffin, white soft paraffin, cetostearyl alcohol, glyceryl monostearate, net price 50 g = £1.69

Excipients include cetostearyl alcohol, fragrance, hydroxybenzoates (parabens), wool fat

Metanium® (Thornton & Ross)

Ointment, titanium dioxide 20%, titanium peroxide 5%, titanium salicylate 3% in a basis containing dimeticone, light liquid paraffin, white soft paraffin, and benzoin tincture, net price 30 g = £2.06

Excipients none as listed in section 13.1.3

Morhulin® (Actavis)

Ointment, cod-liver oil 11.4%, zinc oxide 38%, in a basis containing liquid paraffin and yellow soft paraffin, net price 50 g = £1.91

Excipients include wool fat derivative

Siopel® (Derma UK)

Barrier cream, dimeticone '1000' 10%, cetrimide 0.3%, arachis (peanut) oil, net price 50 g = £2.15

Excipients include butylated hydroxytoluene, cetostearyl alcohol, hydroxybenzoates (parabens)

Sprilon® (Ayrton Saunders)

Spray application, dimeticone 1.04%, zinc oxide 12.5%, in a basis containing wool alcohols, cetostearyl alcohol, dextran, white soft paraffin, liquid paraffin, propellants, net price 115-g pressurised aerosol unit = £8.90

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens), wool fat

Note Flammable

Sudocrem® (Forest)

Cream, benzyl alcohol 0.39%, benzyl benzoate 1.01%, benzyl cinnamate 0.15%, hydrous wool fat (hypoallergenic lanolin) 4%, zinc oxide 15.25%, net price 60 g = £1.45, 125 g = £2.15, 250 g = £3.67, 400 g = £5.25

Excipients include beeswax (synthetic), propylene glycol, butylated hydroxyanisole, fragrance

13.3 Topical antipruritics

Pruritus may be caused by systemic disease (such as obstructive jaundice, endocrine disease, chronic renal disease, iron deficiency, and certain malignant diseases), skin disease (such as eczema, psoriasis, urticaria, and scabies), drug hypersensitivity, or as a side-effect of opioid analgesics. Where possible, the underlying cause should be treated. For the treatment of pruritus in palliative care, see *Prescribing in Palliative Care*, p. 19. Pruritus caused by cholestasis generally requires a bile acid sequestrant (section 1.9.2).

An **emollient** (section 13.2.1) may be of value where the pruritus is associated with dry skin. Preparations containing **calamine** or **crotamiton** are sometimes used but are of uncertain value.

A topical preparation containing **doxepin** 5% is licensed for the relief of pruritus in eczema in children over 12 years; it can cause drowsiness and there may be a risk of sensitisation.

Topical antihistamines and local anaesthetics (section 15.2) are only marginally effective and occasionally cause sensitisation. For *insect stings* and *insect bites*, a short course of a topical corticosteroid is appropriate. Short-term treatment with a **sedating antihistamine** (section 3.4.1) may help in insect stings and in intractable pruritus where sedation is desirable. Calamine preparations are of little value for the treatment of insect stings or bites.

In *pruritus ani*, the underlying cause such as faecal soiling, eczema, psoriasis, or helminth infection should be treated; for preparations used to relieve pruritus ani, see section 1.7.

CALAMINE 

Contra-indications avoid application of preparations containing zinc oxide prior to x-ray (zinc oxide may affect outcome of x-ray)

Indications and dose

Pruritus but see notes above

Calamine (Non-proprietary) 

Aqueous cream, calamine 4%, zinc oxide 3%, liquid paraffin 20%, self-emulsifying glyceryl monostearate 5%, cetomacrogol emulsifying wax 5%, phenox-yethanol 0.5%, freshly boiled and cooled purified water 62.5%, net price 100 mL = £1.19

Lotion (= cutaneous suspension), calamine 15%, zinc oxide 5%, glycerol 5%, bentonite 3%, sodium citrate 0.5%, aqueified phenol 0.5%, in freshly boiled and cooled purified water, net price 200 mL = 81p

Oily lotion (BP 1980), calamine 5%, arachis (peanut) oil 50%, oleic acid 0.5%, wool fat 1%, in calcium hydroxide solution, net price 200 mL = £1.57

CROTAMITON

Cautions avoid use near eyes, in buccal mucosa, or on broken or very inflamed skin; use on doctor's advice for children under 3 years

Contra-indications acute exudative dermatoses

Pregnancy manufacturer advises avoid, especially during the first trimester—no information available

Breast-feeding no information available; avoid application to nipple area

Indications and dose

Pruritus (including pruritus after scabies—section 13.10.4) see notes above

Apply 2–3 times daily (for pruritus after scabies in children under 3 years apply once daily only)

Eurax® (Novartis Consumer Health)

Cream, crotamiton 10%, net price 30 g = £2.38, 100 g = £4.15

Excipients include beeswax, fragrance, hydroxybenzoates (parabens), stearyl alcohol

Lotion, crotamiton 10%, net price 100 mL = £3.14

Excipients include cetyl alcohol, fragrance, propylene glycol, sorbic acid, stearyl alcohol

DOXEPIN HYDROCHLORIDE

Cautions susceptibility to angle-closure glaucoma; urinary retention; mania; cardiac arrhythmias; severe heart disease; avoid application to large areas; **interactions:** Appendix 1 (antidepressants, tricyclic)

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Hepatic impairment manufacturer advises caution in severe liver disease

Pregnancy manufacturer advises use only if potential benefit outweighs risk


Breast-feeding manufacturer advises use only if potential benefit outweighs risk

Side-effects drowsiness; local burning, stinging, irritation, tingling and rash; systemic side-effects such as antimuscarinic effects, headache, fever, dizziness, gastro-intestinal disturbances also reported

Indications and dose**Pruritus in eczema**

Child 12–18 years apply thinly 3–4 times daily; usual max. 3 g per application; usual total max. 12 g daily; coverage should be less than 10% of body surface area

Depressive illness section 4.3.1

Xepin® (CHS) 

Cream, doxepin hydrochloride 5%, net price 30 g = £11.70. Label: 2, 10, patient information leaflet

Excipients include benzyl alcohol

13.4 Topical corticosteroids

Topical corticosteroids are used for the treatment of inflammatory conditions of the skin (other than those arising from an infection), particularly eczema (section 13.5.1), contact dermatitis, insect stings (p. 33), and eczema of scabies (section 13.10.4). Corticosteroids suppress the inflammatory reaction during use; they are not curative and on discontinuation a rebound exacerbation of the condition may occur. They are generally used to relieve symptoms and suppress signs of the disorder when other measures such as emollients are ineffective.

Children, especially infants, are particularly susceptible to side-effects. However, concern about the safety of topical corticosteroids in children should not result in the child being undertreated. The aim is to control the condition as well as possible; inadequate treatment will perpetuate the condition. Carers of young children should be advised that treatment should **not** necessarily be reserved to 'treat only the worst areas' and they may need to be advised that patient information leaflets may contain inappropriate advice for the child's condition.

In an acute flare-up of atopic eczema, it may be appropriate to use more potent formulations of topical corticosteroids for a short period to regain control of the condition. Continuous daily application of a mild corticosteroid such as hydrocortisone 1% is equivalent to a potent corticosteroid such as betamethasone 0.1% applied intermittently.

Topical corticosteroids are not recommended in the routine treatment of *urticaria*; treatment should only be initiated and supervised by a specialist. Topical corticosteroids may worsen ulcerated or secondarily infected lesions. They should not be used indiscriminately in *pruritus* (where they will only benefit if inflammation is causing the itch) and are **not** recommended for *acne vulgaris*.

Systemic or very potent topical corticosteroids should be avoided or given only under specialist supervision in *psoriasis* because, although they may suppress the psoriasis in the short term, relapse or vigorous rebound occurs on withdrawal (sometimes precipitating severe pustular psoriasis). Topical use of potent corticosteroids on widespread psoriasis can lead to systemic as well as to local side-effects. It is reasonable, however, to prescribe a mild topical corticosteroid for a short period (2–4 weeks) for *flexural* and *facial psoriasis*, and to use a more potent corticosteroid such as betamethasone or flucocinonide for *psoriasis of the scalp, palms, or soles* (see below for cautions in psoriasis).

In general, the most potent topical corticosteroids should be reserved for recalcitrant dermatoses such as *chronic discoid lupus erythematosus*, *lichen simplex chronicus*, *hypertrophic lichen planus*, and *palmoplantar pustulosis*. Potent corticosteroids should generally be avoided on the face and skin flexures, but specialists occasionally prescribe them for use on these areas in certain circumstances.

When topical treatment has failed, intralesional corticosteroid injections (section 10.1.2.2) may be used. These are more effective than the very potent topical corticosteroid preparations and should be reserved for severe cases where there are localised lesions such as *keloid scars*, *hypertrophic lichen planus*, or *localised alopecia areata*.

Choice Water-miscible corticosteroid *creams* are suitable for moist or weeping lesions whereas *ointments* are generally chosen for dry, lichenified or scaly lesions or where a more occlusive effect is required. *Lotions* may be useful when minimal application to a large or hair-bearing area is required or for the treatment of exudative lesions. *Occlusive polythene or hydrocolloid dressings* increase absorption, but also increase the risk of side-effects; they are therefore used only under supervision on a short-term basis for areas of very thick skin (such as the palms and soles). Disposable nappies and tight fitting pants also increase the risk of side-effects by increasing absorption of the corticosteroid. The inclusion of urea or salicylic acid also increases the penetration of the corticosteroid.

'Wet-wrap bandaging' (section 13.5.1) increases absorption into the skin, but should be initiated only by a dermatologist and application supervised by a healthcare professional trained in the technique.

In the *BNF for Children*, topical corticosteroids for the skin are categorised as 'mild', 'moderately potent', 'potent' or 'very potent' (see p. 566); the **least potent** preparation which is effective should be chosen but dilution should be avoided whenever possible.

Topical hydrocortisone is usually used in children under 1 year of age. Moderately potent and potent topical corticosteroids should be used with great care in children and for short periods (1–2 weeks) only. A very potent corticosteroid should be initiated under the supervision of a specialist.

Appropriate topical corticosteroids for specific conditions are:

- *insect bites and stings*—mild corticosteroid such as hydrocortisone 1% cream;
- *inflamed nappy rash causing discomfort* in infant over 1 month (section 13.2.2)—mild corticosteroid such as hydrocortisone 0.5% or 1% for up to 7 days (combined with antimicrobial if infected);
- *mild to moderate eczema, flexural and facial eczema or psoriasis*—mild corticosteroid such as hydrocortisone 1%;
- *severe eczema of the face and neck*—moderately potent corticosteroid for 3–5 days only, if not controlled by a mild corticosteroid;
- *severe eczema on the trunk and limbs*—moderately potent or potent corticosteroid for 1–2 weeks only, switching to a less potent preparation as the condition improves;

- *eczema affecting area with thickened skin* (e.g. soles of feet)—potent topical corticosteroid in combination with urea or salicylic acid (to increase penetration of corticosteroid).

Perioral lesions Hydrocortisone cream 1% can be used for up to 7 days to treat uninfected inflammatory lesions on the lips. Hydrocortisone and miconazole cream or ointment is useful where infection by susceptible organisms and inflammation co-exist, particularly for initial treatment (up to 7 days) e.g. in angular cheilitis (see also p. 552). Organisms susceptible to miconazole include *Candida* spp. and many Gram-positive bacteria including streptococci and staphylococci.

Cautions Avoid prolonged use of a topical corticosteroid particularly on the face (and keep away from eyes). Use potent or very potent corticosteroids under specialist supervision; extreme caution is required in dermatoses of infancy including nappy rash—treatment should be limited to 5–7 days.

Psoriasis The use of potent or very potent corticosteroids in psoriasis can result in rebound relapse, development of generalised pustular psoriasis, and local and systemic toxicity, see notes above.

Contra-indications Topical corticosteroids are contra-indicated in untreated bacterial, fungal, or viral skin lesions, in acne, and in perioral dermatitis; potent corticosteroids are contra-indicated in widespread plaque psoriasis (see notes above).

Side-effects *Mild* and *moderately potent* topical corticosteroids are associated with few side-effects but particular care is required when treating neonates and infants, and in the use of *potent* and *very potent* corticosteroids. Absorption through the skin can rarely cause adrenal suppression and even Cushing's syndrome (section 6.3.2), depending on the area of the body being treated and the duration of treatment. Absorption of corticosteroid is greatest from severely inflamed skin, thin skin (especially on the face or genital area), from flexural sites (e.g. axillae, groin), and in infants where skin surface area is higher in relation to body-weight; absorption is increased by occlusion. Local side-effects include:

- spread and worsening of untreated infection;
- thinning of the skin which may be restored over a period after stopping treatment but the original structure may never return;
- irreversible striae atrophicae and telangiectasia;
- contact dermatitis;
- perioral dermatitis;
- acne, or worsening of acne or rosacea;
- mild depigmentation which may be reversible;
- hypertrichosis also reported.

Children and their carers should be reassured that side effects such as skin thinning and systemic effects rarely occur when topical corticosteroids are used appropriately.

Safe Practice

In order to minimise the side-effects of a topical corticosteroid, it is important to apply it **thinly** to affected areas **only**, no more frequently than **twice daily**, and to use the least potent formulation which is fully effective.

Application Topical corticosteroid preparations should be applied no more frequently than twice daily; once daily is often sufficient.

Topical corticosteroids should be spread thinly on the skin but in sufficient quantity to cover the affected areas. The length of cream or ointment expelled from a tube may be used to specify the quantity to be applied to a given area of skin. This length can be measured in terms of a *fingertip unit* (the distance from the tip of the adult index finger to the first crease). One fingertip unit (approximately 500 mg from a tube with a standard 5-mm diameter nozzle) is sufficient to cover an area that is twice that of the flat adult handprint (palm and fingers).

If a child is using topical corticosteroids of different potencies, the child and their carers should be told when to use each corticosteroid. The potency of each topical corticosteroid (see Topical Corticosteroid Preparation Potencies, p. 566) should be included on the label with the directions for use. The label should be attached to the container (for example, the tube) rather than the outer packaging.

Mixing topical preparations on the skin should be avoided where possible; several minutes should elapse between application of different preparations.

Compound preparations The advantages of including other substances (such as antibacterials or antifungals) with corticosteroids in topical preparations are uncertain, but such combinations may have a place where inflammatory skin conditions are associated with bacterial or fungal infection, such as infected eczema. In these cases the antimicrobial drug should be chosen according to the sensitivity of the infecting organism and used regularly for a short period (typically twice daily for 1 week). Longer use increases the likelihood of resistance and of sensitisation.

The keratolytic effect of salicylic acid facilitates the absorption of topical corticosteroids; however, excessive and prolonged use of topical preparations containing salicylic acid may cause salicylism.

Topical corticosteroid potencies

Potency of a topical corticosteroid preparation depends upon the formulation as well as the corticosteroid. Therefore, proprietary names are shown below.

Mild

Hydrocortisone 0.1–2.5%, *Dioderm*, *Mildison*, *Synalar 1 in 10 Dilution*

Mild with antimicrobials *Canesten HC*, *Daktacort*, *Econacort*, *Fucidin H*, *Nystaform-HC*, *Terra-Cortril*, *Timodine*

Mild with cromatolone *Eurax-Hydrocortisone*

Moderate

Betnovate-RD, *Eumovate*, *Haelan*, *Modrasone*, *Synalar 1 in 4 Dilution*, *Ultralanum Plain*

Moderate with antimicrobials *Trimovate*

Moderate with urea *Alphaderm*, *Calmurid HC*

Potent

Beclomethasone dipropionate 0.025%, Betamethasone valerate 0.1%, *Betacap*, *Betamousse*, *Betnovate*, *Cutivate*, *Diprosone*, *Elocon*, Hydrocortisone butyrate, *Locoid*, *Locoid Crelo*, *Metosyn*, Mometasone furoate 0.1%, *Nerisone*, *Synalar*

Potent with antimicrobials *Aureocort*, Betamethasone and clioquinol, *Betamethasone* and neomycin, *Fucibet*, *Lotiderm*, *Synalar C*, *Synalar N*

Potent with salicylic acid *Diprosalic*

Very potent

Dermovate, *Nerisone Forte*

Very potent with antimicrobials Clobetasol propionate 0.05% with neomycin and nystatin

HYDROCORTISONE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Indications and dose

Mild inflammatory skin disorders such as eczema (but for over-the-counter preparations, see below); nappy rash (see also section 13.2.2)

Apply thinly 1–2 times daily

Hydrocortisone (Non-proprietary) **[PoM]**

Cream, hydrocortisone 0.5%, net price, 15 g = £1.31, 30 g = £2.96; 1%, 15 g = £1.04, 30 g = £2.08, 50 g = £3.47; 2.5%, 15 g = £23.92. Label: 28, counselling, application, see p. 566. Potency: mild

Dental prescribing on NHS Hydrocortisone Cream 1% 15 g may be prescribed

Ointment, hydrocortisone 0.5%, net price 15 g = £3.77, 30 g = £4.90; 1%, 15 g = £1.10, 30 g = £2.20, 50 g = £3.67; 2.5%, 15 g = £23.72. Label: 28, counselling, application, see p. 566. Potency: mild
When hydrocortisone cream or ointment is prescribed and no strength is stated, the 1% strength should be supplied

Over-the-counter hydrocortisone preparations

Skin creams and ointments containing hydrocortisone (alone or with other ingredients) can be sold to the public for the treatment of allergic contact dermatitis, irritant dermatitis, insect bite reactions and mild to moderate eczema in children over 10 years, to be applied sparingly over the affected area 1–2 times daily for max. 1 week. Over-the-counter hydrocortisone preparations should not be sold without medical advice for children under 10 years or for pregnant women; they should **not** be sold for application to the face, anogenital region, broken or infected skin (including cold sores, acne, and athlete's foot); over-the-counter hydrocortisone preparations containing clotrimazole or miconazole nitrate can be sold to the public for treatment of athlete's foot and candidal intertrigo

Proprietary hydrocortisone preparations

Dioderm® (Derma) **[PoM]**

Cream, hydrocortisone 0.1%, net price 30 g = £2.39. Label: 28, counselling, application, see p. 566.

Potency: mild

Excipients include cetostearyl alcohol, propylene glycol

Note Although this contains only 0.1% hydrocortisone, the formulation is designed to provide a clinical activity comparable to that of Hydrocortisone Cream 1% BP

Mildison® (Astellas) **[PoM]**

Lipocream, hydrocortisone 1%, net price 30 g = £1.71. Label: 28, counselling, application, see p. 566.

Potency: mild

Excipients include benzyl alcohol, cetostearyl alcohol, hydroxybenzoates (parabens)

Compound preparations

Compound preparations with coal tar, see section 13.5.2

Alphaderm® (Alliance) (PoM)

Cream, hydrocortisone 1%, urea 10%, net price 30 g = £2.38; 100 g = £7.03. Label: 28, counselling, application, see p. 566. Potency: moderate
Excipients none as listed in section 13.1.3

Calmurid HC® (Galderma) (PoM)

Cream, hydrocortisone 1%, urea 10%, lactic acid 5%, net price 100 g = £10.51. Label: 28, counselling, application, see p. 566. Potency: moderate
Excipients none as listed in section 13.1.3

Note If stinging occurs, manufacturer advises dilute to half-strength with aqueous cream for 1 week then transfer to undiluted preparation (but see section 13.1.1 for advice to avoid dilution where possible)

With antimicrobials

See notes above for comment on compound preparations

Canesten HC® (Bayer Consumer Care) (PoM)

Cream, hydrocortisone 1%, clotrimazole 1%, net price 30 g = £2.42. Label: 28, counselling, application, see p. 566. Potency: mild

Excipients include benzyl alcohol, cetostearyl alcohol

Note A 15-g tube is on sale to the public for the treatment of athlete's foot and fungal infection of skin folds with associated inflammation in children 10–18 years

Daktacort® (Janssen) (PoM)

Cream, hydrocortisone 1%, miconazole nitrate 2%, net price 30 g = £2.49. Label: 28, counselling, application, see p. 566. Potency: mild

Excipients include butylated hydroxyanisole, disodium edetate

Cautions interactions: Appendix 1 (antifungals, imidazole)

Dental prescribing on NHS May be prescribed as Miconazole and Hydrocortisone Cream for max. 7 days

Note A 15-g tube is on sale to the public for the treatment of athlete's foot and candidal intertrigo in children 10–18 years

Ointment, hydrocortisone 1%, miconazole nitrate 2%, net price 30 g = £2.50. Label: 28, counselling, application, see p. 566. Potency: mild

Excipients none as listed in section 13.1.3

Cautions interactions: Appendix 1 (antifungals, imidazole)

Dental prescribing on NHS May be prescribed as Miconazole and Hydrocortisone Ointment for max. 7 days

Fucidin H® (LEO) (PoM)

Cream, hydrocortisone acetate 1%, fusidic acid 2%, net price 30 g = £5.02, 60 g = £10.04. Label: 28, counselling, application, see p. 566. Potency: mild

Excipients include butylated hydroxyanisole, cetyl alcohol, polysorbate 60, potassium sorbate

Nystaform-HC® (Typharm) (PoM)

Cream, hydrocortisone 0.5%, nystatin 100 000 units/g, chlorhexidine hydrochloride 1%, net price 30 g = £2.66. Label: 28, counselling, application, see p. 566. Potency: mild

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbate '60'

Ointment, hydrocortisone 1%, nystatin 100 000 units/g, chlorhexidine acetate 1%, net price 30 g = £2.66. Label: 28, counselling, application, see p. 566. Potency: mild

Excipients none as listed in section 13.1.3

Terra-Cortril® (Alliance) (PoM)

Ointment, hydrocortisone 1%, oxytetracycline (as hydrochloride) 3%, net price 30 g = £5.01. Label: 28, counselling, application, see p. 566. Potency: mild

Excipients none as listed in section 13.1.3

Contra-indications children under 12 years

Pregnancy section 5.1.3

Breast-feeding section 5.1.3

Timodine® (Alliance) (PoM)

Cream, hydrocortisone 0.5%, nystatin 100 000 units/g, benzalkonium chloride solution 0.2%, dimeticone '350' 10%, net price 30 g = £2.86. Label: 28, counselling, application, see p. 566. Potency: mild

Excipients include butylated hydroxyanisole, cetostearyl alcohol, hydroxybenzoates (parabens), sodium metabisulfite, sorbic acid

HYDROCORTISONE BUTYRATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Indications and dose

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Child 1–18 years apply thinly 1–2 times daily

Locoid® (Astellas) (PoM)

Cream, hydrocortisone butyrate 0.1%, net price 30 g = £1.60, 100 g = £4.93. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Lipocream, hydrocortisone butyrate 0.1%, net price 30 g = £1.69, 100 g = £5.17. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include benzyl alcohol, cetostearyl alcohol, hydroxybenzoates (parabens)

Note For bland cream basis see *Lipobase®*, section 13.2.1

Ointment, hydrocortisone butyrate 0.1%, net price 30 g = £1.60, 100 g = £4.93. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients none as listed in section 13.1.3

Scalp lotion, hydrocortisone butyrate 0.1%, in an aqueous isopropyl alcohol basis, net price 100 mL = £6.83. Label: 15, 28, counselling, application, see p. 566. Potency: potent

Excipients none as listed in section 13.1.3

Locoid Crelo® (Astellas) (PoM)

Lotion (topical emulsion), hydrocortisone butyrate 0.1% in a water-miscible basis, net price 100 g (with applicator nozzle) = £5.91. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include butylated hydroxytoluene, cetostearyl alcohol, hydroxybenzoates (parabens), propylene glycol

ALCLOMETASONE DIPROPIONATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Inflammatory skin disorders such as eczemas

Apply thinly 1–2 times daily

Modrasone® (TEVA UK) (PoM)

Cream, alclometasone dipropionate 0.05%, net price 50 g = £2.68. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include cetostearyl alcohol, chlorocresol, propylene glycol

BECLOMETASONE DIPROPIONATE

(Beclometasone dipropionate)

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 1 year

Indications and dose

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

Beclometasone (Non-proprietary) (PoM)

Cream, beclometasone dipropionate 0.025%, net price 30 g = £68.00. Label: 28, counselling, application, see p. 566. Potency: potent

Ointment, beclometasone dipropionate 0.025%, net price 30 g = £68.00. Label: 28, counselling, application, see p. 566. Potency: potent

BETAMETHASONE ESTERS

Cautions see notes above; use of more than 100 g per week of 0.1% preparation likely to cause adrenal suppression

Contra-indications see notes above

Side-effects see notes above

Licensed use *Betacap®*, Betamethasone and clioquinol preparations, *Betnovate®*, and *Betnovate-RD®* not licensed for use in children under 1 year; *Bettamousse®* and *Fucibet® Lipid Cream* not licensed for use in children under 6 years; Betamethasone and neomycin preparations not licensed for use in children under 2 years; *Lotiderm®* not licensed for use in children under 12 years; *all other preparations* licensed for use in children (age range not specified by manufacturer)

Indications and dose

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

Betamethasone Valerate (Non-proprietary) (PoM)

Cream, betamethasone (as valerate) 0.1%, net price 30 g = £2.84, 100 g = £9.47. Label: 28, counselling, application, see p. 566. Potency: potent

Ointment, betamethasone (as valerate) 0.1%, net price 30 g = £2.24, 100 g = £7.47. Label: 28, counselling, application, see p. 566. Potency: potent

Betacap® (Dermal) (PoM)

Scalp application, betamethasone (as valerate) 0.1% in a water-miscible basis containing coconut oil derivative, net price 100 mL = £3.75. Label: 15, 28, counselling, application, see p. 566. Potency: potent

Excipients none as listed in section 13.1.3

Betnovate® (GSK) (PoM)

Cream, betamethasone (as valerate) 0.1% in a water-miscible basis, net price 30 g = £1.43, 100 g = £4.05. Label: 28, counselling, application, see p. 566.

Potency: potent

Excipients include cetostearyl alcohol, chlorocresol

Ointment, betamethasone (as valerate) 0.1% in an anhydrous paraffin basis, net price 30 g = £1.43, 100 g = £4.05. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients none as listed in section 13.1.3

Lotion, betamethasone (as valerate) 0.1%, net price 100 mL = £4.58. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Scalp application, betamethasone (as valerate) 0.1% in a water-miscible basis, net price 100 mL = £4.99. Label: 15, 28, counselling, application, see p. 566.

Potency: potent

Excipients none as listed in section 13.1.3

Betnovate-RD® (GSK) (PoM)

Cream, betamethasone (as valerate) 0.025% in a water-miscible basis (1 in 4 dilution of *Betnovate®* cream), net price 100 g = £3.15. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include cetostearyl alcohol, chlorocresol

Ointment, betamethasone (as valerate) 0.025% in an anhydrous paraffin basis (1 in 4 dilution of *Betnovate®* ointment), net price 100 g = £3.15. Label: 28, counselling, application, see p. 566.

Potency: moderate

Excipients none as listed in section 13.1.3

Bettamousse® (RPH) (PoM)

Foam (= scalp application), betamethasone valerate 0.12% (= betamethasone 0.1%), net price 100 g = £9.75. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include cetyl alcohol, polysorbate 60, propylene glycol, stearyl alcohol

Note Flammable

Diprosone® (MSD) (PoM)

Cream, betamethasone (as dipropionate) 0.05%, net price 30 g = £2.16, 100 g = £6.12. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include cetostearyl alcohol, chlorocresol

Ointment, betamethasone (as dipropionate) 0.05%, net price 30 g = £2.16, 100 g = £6.12. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients none as listed in section 13.1.3

Lotion, betamethasone (as dipropionate) 0.05%, net price 30 mL = £2.73, 100 mL = £7.80. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients none as listed in section 13.1.3

With salicylic acid

See notes above for comment on compound preparations
For prescribing information on salicylic acid, see p. 577

Diprosalic® (MSD) (PoM)

Ointment, betamethasone (as dipropionate) 0.05%, salicylic acid 3%, net price 30 g = £3.18, 100 g = £9.14. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients none as listed in section 13.1.3

Dose

Apply thinly 1–2 times daily

Scalp application, betamethasone (as dipropionate) 0.05%, salicylic acid 2%, in an alcoholic basis, net price 100 mL = £10.10. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include disodium edetate

Dose

Apply a few drops 1–2 times daily

■ With antimicrobials

See notes above for comment on compound preparations

Betamethasone and clioquinol (Non-proprietary) (PoM)

Cream, betamethasone (as valerate) 0.1%, clioquinol 3%, net price 30 g = £9.48. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients may include cetostearyl alcohol, chlorocresol

Note Stains clothing

Ointment, betamethasone (as valerate) 0.1%, clioquinol 3%, net price 30 g = £9.48. Label: 28, counselling, application, see p. 566. Potency: potent

Note Stains clothing

Betamethasone and neomycin (Non-proprietary) (PoM)

Cream, betamethasone (as valerate) 0.1%, neomycin sulfate 0.5%, net price 30 g = £9.48, 100 g = £28.01. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients may include cetostearyl alcohol, chlorocresol

Ointment, betamethasone (as valerate) 0.1%, neomycin sulfate 0.5%, net price 30 g = £9.48, 100 g = £28.01. Label: 28, counselling, application, see p. 566. Potency: potent

Fucibet® (LEO) (PoM)

Cream, betamethasone (as valerate) 0.1%, fusidic acid 2%, net price 30 g = £5.32, 60 g = £10.63. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include cetostearyl alcohol, chlorocresol

Lipid cream, betamethasone (as valerate) 0.1%, fusidic acid 2%, net price 30 g = £5.62. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Lotiderm® (TEVA UK) (PoM)

Cream, betamethasone dipropionate 0.064% (= betamethasone 0.05%), clotrimazole 1%, net price 30 g = £6.34. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include benzyl alcohol, cetostearyl alcohol, propylene glycol

CLOBETASOL PROPIONATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use *Dermovate*® not licensed for use in children under 1 year; Clobetasol with neomycin and nystatin preparations not licensed for use in children under 2 years

Indications and dose

Short-term treatment only of severe resistant inflammatory skin disorders such as recalcitrant eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily for up to 4 weeks

Dermovate® (GSK) (PoM)

Cream, clobetasol propionate 0.05%, net price 30 g = £2.69, 100 g = £7.90. Label: 28, counselling, application, see p. 566. Potency: very potent

Excipients include beeswax (or beeswax substitute), cetostearyl alcohol, chlorocresol, propylene glycol

Ointment, clobetasol propionate 0.05%, net price 30 g = £2.69, 100 g = £7.90. Label: 28, counselling, application, see p. 566. Potency: very potent

Excipients include propylene glycol

Scalp application, clobetasol propionate 0.05%, in a thickened alcoholic basis, net price 30 mL = £3.07, 100 mL = £10.42. Label: 15, 28, counselling, application, see p. 566. Potency: very potent

Excipients none as listed in section 13.1.3

■ With antimicrobials

See notes above for comment on compound preparations

Clobetasol with neomycin and nystatin (Non-proprietary) (PoM)

Cream, clobetasol propionate 0.05%, neomycin sulfate 0.5%, nystatin 100 000 units/g, net price 30 g = £64.00. Label: 28, counselling, application, see p. 566. Potency: very potent

Ointment, clobetasol propionate 0.05%, neomycin sulfate 0.5%, nystatin 100 000 units/g, in a paraffin basis, net price 30 g = £64.00. Label: 28, counselling, application, see p. 566. Potency: very potent

CLOBETASONE BUTYRATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Eczemas and dermatitis of all types; maintenance between courses of more potent corticosteroids

Apply thinly 1–2 times daily

1 Eumovate® (GSK) (PoM)

Cream, clobetasone butyrate 0.05%, net price 30 g = £1.86, 100 g = £5.44. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include beeswax substitute, cetostearyl alcohol, chlorocresol

Ointment, clobetasone butyrate 0.05%, net price 30 g = £1.86, 100 g = £5.44. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients none as listed in section 13.1.3

■ With antimicrobials

See notes above for comment on compound preparations

Trimovate® (GSK) (PoM)

Cream, clobetasone butyrate 0.05%, oxytetracycline 3% (as calcium salt), nystatin 100 000 units/g, net price 30 g = £3.29. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include cetostearyl alcohol, chlorocresol, sodium metabisulfite

Note Stains clothing

1. Cream can be sold to the public for short-term symptomatic treatment and control of patches of eczema and dermatitis (but not seborrhoeic dermatitis) in children over 12 years provided pack does not contain more than 15 g

DIFLUCORTOLONE VALERATE**Cautions** see notes above**Contra-indications** see notes above**Side-effects** see notes above**Licensed use** *Nerisone*® licensed for use in children (age range not specified by manufacturer); *Nerisone Forte*® not licensed for use in children under 4 years**Indications and dose**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids; high strength (0.3%), short-term treatment of severe exacerbations, psoriasis see notes above

Apply thinly 1–2 times daily for up to 4 weeks (0.1% preparations) or 2 weeks (0.3% preparations), reducing strength as condition responds

Nerisone® (Meadow) (PoM)

Cream, diflucortolone valerate 0.1%, net price 30 g = £1.59. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include disodium edetate, hydroxybenzoates (parabens), stearyl alcohol

Oily cream, diflucortolone valerate 0.1%, net price 30 g = £2.56. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include beeswax

Ointment, diflucortolone valerate 0.1%, net price 30 g = £1.59. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients none as listed in section 13.1.3

Nerisone Forte® (Meadow) (PoM)

Oily cream, diflucortolone valerate 0.3%, net price 15 g = £2.09. Label: 28, counselling, application, see p. 566. Potency: very potent

Excipients include beeswax

Ointment, diflucortolone valerate 0.3%, net price 15 g = £2.09. Label: 28, counselling, application, see p. 566. Potency: very potent

Excipients none as listed in section 13.1.3

FLUDROXYCORTIDE
(Flurandrenolone)**Cautions** see notes above**Contra-indications** see notes above**Side-effects** see notes above**Licensed use** licensed for use in children (age range not specified by manufacturer)**Indications and dose**

Inflammatory skin disorders such as eczemas
Apply thinly 1–2 times daily

Haelan® (Typharm) (PoM)

Cream, fludroxycortide 0.0125%, net price 60 g = £3.26. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include cetyl alcohol, propylene glycol

Ointment, fludroxycortide 0.0125%, net price 60 g = £3.26. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include beeswax, cetyl alcohol, polysorbate

Tape, polythene adhesive film impregnated with fludroxycortide 4 micrograms/cm², net price 7.5 cm × 50 cm = £9.27, 7.5 cm × 200 cm = £24.95

Dose

Chronic localised recalcitrant dermatoses (but not acute or weeping)

Cut tape to fit lesion, apply to clean, dry skin shorn of hair, usually for 12 hours daily

FLUOCINOLONE ACETONIDE**Cautions** see notes above**Contra-indications** see notes above**Side-effects** see notes above**Licensed use** not licensed for use in children under 1 year**Indications and dose**

Severe inflammatory skin disorders such as eczemas, psoriasis see notes above

Apply thinly 1–2 times daily, reducing strength as condition responds

Synalar® (GP Pharma) (PoM)

Cream, fluocinolone acetonide 0.025%, net price 30 g = £4.14, 100 g = £11.75. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates, propylene glycol

Gel, fluocinolone acetonide 0.025%, net price 30 g = £5.56. For use on scalp and other hairy areas. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include hydroxybenzoates (parabens), propylene glycol

Ointment, fluocinolone acetonide 0.025%, net price 30 g = £4.14, 100 g = £11.75. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include propylene glycol, wool fat

Synalar 1 in 4 Dilution® (GP Pharma) (PoM)

Cream, fluocinolone acetonide 0.00625%, net price 50 g = £4.84. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates, propylene glycol

Ointment, fluocinolone acetonide 0.00625%, net price 50 g = £4.84. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include propylene glycol, wool fat

Synalar 1 in 10 Dilution® (GP Pharma) (PoM)

Cream, fluocinolone acetonide 0.0025%, net price 50 g = £4.58. Label: 28, counselling, application, see p. 566. Potency: mild

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates, propylene glycol

With antibacterials

See notes above for comment on compound preparations

Synalar C® (GP Pharma) (PoM)

Cream, fluocinolone acetonide 0.025%, clioquinol 3%, net price 15 g = £2.66. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include cetostearyl alcohol, disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol

Ointment, fluocinolone acetonide 0.025%, clioquinol 3%, net price 15 g = £2.66. Label: 28, counselling, application, see p. 566. Potency: potent

Note stains clothing

Excipients include propylene glycol, wool fat

Synalar N[®] (GP Pharma) (PoM)

Cream, fluocinonide acetonide 0.025%, neomycin sulfate 0.5%, net price 30 g = £4.36. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens), polysorbates, propylene glycol

Ointment, fluocinonide acetonide 0.025%, neomycin sulfate 0.5%, in a greasy basis, net price 30 g = £4.36. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include propylene glycol, wool fat

FLUOCINONIDE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 1 year

Indications and dose

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

Mometan[®] (GP Pharma) (PoM)

FAPG cream, fluocinonide 0.05%, net price 25 g = £3.96, 100 g = £13.34. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include propylene glycol

Ointment, fluocinonide 0.05%, net price 25 g = £3.50, 100 g = £13.15. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include propylene glycol, wool fat

FLUOCORTOLONE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

Ultralanum Plain[®] (Meadow) (PoM)

Cream, fluocortolone caproate 0.25%, fluocortolone pivalate 0.25%, net price 50 g = £2.95. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include disodium edetate, fragrance, hydroxybenzoates (parabens), stearyl alcohol

Ointment, fluocortolone 0.25%, fluocortolone caproate 0.25%, net price 50 g = £2.95. Label: 28, counselling, application, see p. 566. Potency: moderate

Excipients include wool fat, fragrance

FLUTICASONE PROPIONATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 3 months

Indications and dose

Inflammatory skin disorders such as dermatitis and eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

Cutivate[®] (GSK) (PoM)

Cream, fluticasone propionate 0.05%, net price 15 g = £2.27, 30 g = £4.24. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include cetostearyl alcohol, imidurea, propylene glycol

Ointment, fluticasone propionate 0.005%, net price 15 g = £2.27, 30 g = £4.24. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include propylene glycol

MOMETASONE FUROATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 2 years

Indications and dose

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly once daily (to scalp in case of lotion)

Mometasone (Non-proprietary) (PoM)

Ointment, mometasone furoate 0.1%, net price 30 g = £3.24, 100 g = £10.80. Label: 28, counselling, application, see p. 566. Potency: potent

Elocon[®] (MSD) (PoM)

Cream, mometasone furoate 0.1%, net price 30 g = £4.36, 100 g = £12.58. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include beeswax

Ointment, mometasone furoate 0.1%, net price 30 g = £4.32, 100 g = £12.44. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include beeswax, propylene glycol

Scalp lotion, mometasone furoate 0.1% in an aqueous isopropyl alcohol basis, net price 30 mL = £4.36. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include propylene glycol

TRIAMCINOLONE ACETONIDE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use *Aureocort[®]* not licensed for use in children under 8 years

Indications and dose

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

With antimicrobials

See notes above for comment on compound preparations

Aureocort® (AMCO) (PoM)

Ointment, triamcinolone acetonide 0.1%, chlortetracycline hydrochloride 3%, in an anhydrous greasy basis containing wool fat and white soft paraffin, net price 15 g = £3.51. Label: 28, counselling, application, see p. 566. Potency: potent

Excipients include wool fat

Note Stains clothing

13.5 Preparations for eczema and psoriasis

13.5.1 Preparations for eczema

13.5.2 Preparations for psoriasis

13.5.3 Drugs affecting the immune response

13.5.1 Preparations for eczema

The main types of eczema (dermatitis) in children are atopic, irritant and allergic contact; different types may co-exist. *Atopic eczema* is the most common type and it usually involves dry skin as well as infection and lichenification caused by scratching and rubbing. *Seborrhoeic dermatitis* (see below) is also common in infants.

Management of eczema involves the removal or treatment of contributory factors; known or suspected irritants and contact allergens should be avoided. Rarely, ingredients in topical medicinal products may sensitise the skin (section 13.1.3); *BNF for Children* lists active ingredients together with excipients that have been associated with skin sensitisation.

Skin dryness and the consequent irritant eczema requires **emollients** (section 13.2.1) applied regularly (at least twice daily) and liberally to the affected area; this can be supplemented with bath or shower emollients. The use of emollients should continue even if the eczema improves or if other treatment is being used.

Topical corticosteroids (section 13.4) are also required in the management of eczema; the potency of the corticosteroid should be appropriate to the severity and site of the condition, and the age of the child. Mild corticosteroids are generally used on the face and on flexures; the more potent corticosteroids are generally required for use on lichenified areas of eczema or for severe eczema on the scalp, limbs, and trunk. Treatment should be reviewed regularly, especially if a potent corticosteroid is required. In children with frequent flares (2–3 per month), a topical corticosteroid can be applied on 2 consecutive days each week to prevent further flares.

Bandages (including those containing **zinc** and **ichthammol**) are sometimes applied over topical corticosteroids or emollients to treat eczema of the limbs. Dry-wrap dressings can be used to provide a physical barrier to help prevent scratching and improve retention of emollients. Wet elasticated viscose stockinette is used for 'wet-wrap' bandaging over topical corticosteroids or emollients to cool the skin and relieve itching, but there is an increased risk of infection and excessive absorption of the corticosteroid; 'wet-wrap' bandaging should be used under specialist supervision.

For details of elasticated viscose stockinette tubular bandages and garments, and silk clothing, see BNFC section A5.8.3

For the role of topical **pimecrolimus** and **tacrolimus** in atopic eczema, see section 13.5.3.

Infection Bacterial infection (commonly with *Staphylococcus aureus* and occasionally with *Streptococcus pyogenes*) can exacerbate eczema. A topical antibacterial (section 13.10.1) may be used for small areas of mild infection; treatment should be limited to a short course (typically 1 week) to reduce the risk of drug resistance or skin sensitisation. Associated eczema is treated simultaneously with a topical corticosteroid which can be combined with a topical antimicrobial.

Eczema involving moderate to severe, widespread, or recurrent infection requires the use of a systemic antibacterial (section 5.1, table 1) that is active against the infecting organism. Preparations that combine an antiseptic with an emollient application (section 13.2.1) and with a bath emollient (section 13.2.1.1) can also be used; antiseptic shampoos (section 13.9) can be used on the scalp.

Intertriginous eczema commonly involves candida and bacteria; it is best treated with a mild or moderately potent topical corticosteroid combined with a suitable antimicrobial drug. For the treatment of nappy rash, see section 13.2.2.

Widespread *herpes simplex infection* may complicate atopic eczema (eczema herpeticum) and treatment under specialist supervision with a systemic antiviral drug (section 5.3.2.1) is indicated. Secondary bacterial infection often exacerbates eczema herpeticum.

The management of *seborrhoeic dermatitis* is described below.

Management of other features of eczema

Lichenification, which results from repeated scratching, is treated initially with a potent corticosteroid. Bandages containing **ichthammol** (to reduce pruritus) and other substances such as **zinc oxide** can be applied over the corticosteroid or emollient. **Coal tar** (section 13.5.2) and **ichthammol** can be useful in some cases of *chronic eczema*. **Discoid eczema**, with thickened plaques in chronic atopic eczema, is usually treated with a topical antiseptic preparation, a potent topical corticosteroid, and paste bandages containing zinc oxide and **ichthammol**.

A *non-sedating* antihistamine (section 3.4.1) may be of some value in relieving severe itching or urticaria associated with eczema. A *sedating* antihistamine (section 3.4.1) can be used at night if itching causes sleep disturbance, but a large dose may be needed and drowsiness may persist on the following day.

Exudative ('weeping') eczema requires a potent corticosteroid initially; infection may also be present and require specific treatment (see above). **Potassium permanganate** solution (1 in 10 000) can be used as a soak in exudating eczema for its antiseptic and astringent effects; treatment should be stopped when exudation stops.

Severe refractory eczema is best managed under specialist supervision; it may require phototherapy or drugs that act on the immune system (section 13.5.3).

Seborrhoeic dermatitis *Seborrhoeic dermatitis* (*seborrhoeic eczema*) is associated with species of the yeast *Malassezia*. *Infantile seborrhoeic dermatitis* affects

particularly the body folds, nappy area and scalp; it is treated with emollients and mild topical corticosteroids with suitable antimicrobials. Infantile seborrhoeic dermatitis affecting the scalp (*cradle cap*) is treated by hydrating the scalp using natural oils and the use of mild shampoo (section 13.9).

In older children, seborrhoeic dermatitis affects the scalp, paranasal areas, and eyebrows. Shampoos active against the yeast (including those containing ketoconazole and coal tar, section 13.9) and combinations of mild topical corticosteroids with suitable antimicrobials (section 13.4) are used to treat older children.

ICHTHAMMOL

Side-effects skin irritation

Licensed use no information available

Indications and dose

Chronic lichenified eczema

Child 1–18 years apply 1–3 times daily

Ichthammol Ointment, BP 1980

Ointment, ichthammol 10%, yellow soft paraffin 45%, wool fat 45%

Zinc and Ichthammol Cream, BP

Cream, ichthammol 5%, cetostearyl alcohol 3%, wool fat 10%, in zinc cream

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Medicated bandages

Zinc paste bandages are used with **coal tar** or **ichthammol** in chronic lichenified skin conditions such as chronic eczema (ichthammol often being preferred since its action is considered to be milder). They are also used with **calamine** in milder eczematous skin conditions.

For information on available medicated bandages and stockings, see BNF Appendix 5.

13.5.2 Preparations for psoriasis

Psoriasis is characterised by epidermal thickening and scaling. It commonly affects extensor surfaces and the scalp. For mild psoriasis, reassurance and treatment with an emollient may be all that is necessary. *Guttate psoriasis* is a distinctive form of psoriasis that characteristically occurs in children and young adults, often following a streptococcal throat infection or tonsillitis.

Occasionally psoriasis is provoked or exacerbated by drugs such as lithium, chloroquine and hydroxychloroquine, beta-blockers, non-steroidal anti-inflammatory drugs, and ACE inhibitors. Psoriasis may not occur until the drug has been taken for weeks or months.

Emollients (section 13.2.1), in addition to their effects on dryness, scaling and cracking, may have an anti-proliferative effect in psoriasis. They are particularly useful in *inflammatory psoriasis* and in *chronic stable plaque psoriasis*.

For *chronic stable plaque psoriasis* on extensor surfaces of trunk and limbs preparations containing **coal tar** are moderately effective, but the smell is unacceptable to some children. **Vitamin D** and its analogues are effective and cosmetically acceptable alternatives to preparations containing coal tar or dithranol. **Dithranol** is

an effective topical antipsoriatic agent but it irritates and stains the skin and it should be used only under specialist supervision. Adverse effects of dithranol are minimised by using a 'short-contact technique' (see below) and by starting with low concentration preparations. **Tazarotene**, a topical retinoid for the treatment of mild to moderate plaque psoriasis, is not recommended for use in children under 18 years. These medications can irritate the skin particularly in the flexures and they are not suitable for the more inflammatory forms of psoriasis; their use should be suspended during an inflammatory phase of psoriasis. The efficacy and the irritancy of each substance varies between patients. If a substance irritates significantly, it should be stopped or the concentration reduced; if it is tolerated, its effects should be assessed after 4 to 6 weeks and treatment continued if it is effective.

Widespread *unstable psoriasis* of erythrodermic or generalised pustular type requires urgent specialist assessment. Initial topical treatment should be limited to using emollients frequently and generously. More localised acute or subacute *inflammatory psoriasis* with hot, spreading or itchy lesions, should be treated topically with emollients or with a corticosteroid of moderate potency.

Scalp psoriasis is usually scaly, and the scale may be thick and adherent. This requires softening with an emollient ointment, cream, or oil and usually combined with **salicylic acid** as a keratolytic.

Some preparations for psoriasis affecting the scalp combine salicylic acid with coal tar or **sulfur**. The preparation should be applied generously and left on for at least an hour, often more conveniently overnight, before washing it off. If a corticosteroid lotion or gel is required (e.g. for itch), it can be used in the morning.

Flexural psoriasis can be managed with short-term use of a mild potency topical corticosteroid. **Calcitriol** or **tacalcitol** can be used in the longer term; **calcipotriol** is more likely to cause irritation in flexures and should be avoided. Low-strength tar preparations can also be used.

Facial psoriasis can be treated with short-term use of a mild topical corticosteroid; if this is ineffective, calcitriol, tacalcitol, or a low-strength tar preparation can be used.

Calcipotriol and **tacalcitol** are analogues of vitamin D that affect cell division and differentiation. **Calcitriol** is an active form of vitamin D. Vitamin D and its analogues are used as first-line treatment for plaque psoriasis; they do not smell or stain and they may be more acceptable than tar or dithranol products. Of the vitamin D analogues, tacalcitol and calcitriol are less likely to irritate.

Coal tar has anti-inflammatory properties that are useful in chronic plaque psoriasis; it also has antiscaling properties. Contact of coal tar products with normal skin is not normally harmful and preparations containing coal tar can be used for widespread small lesions; however, irritation, contact allergy, and sterile folliculitis can occur. Leave-on preparations that remain in contact with the skin, such as creams or ointments, containing up to 6% coal tar may be used on children 1 month to 2 years; leave-on preparations containing coal tar 10% may be used on children over 2 years with more severe psoriasis. Tar baths and tar shampoos (see section 13.9) may also be helpful.

Dithranol is effective for chronic plaque psoriasis. Its major disadvantages are irritation (for which individual susceptibility varies) and staining of skin and of clothing. It should be applied to chronic extensor plaques only, carefully avoiding normal skin. Dithranol is not generally suitable for widespread small lesions nor should it be used in the flexures or on the face. Treatment should be started with a low concentration such as dithranol 0.1%, and the strength increased gradually every few days up to 3%, according to tolerance. Proprietary preparations are more suitable for home use; they are usually washed off after 20–30 minutes ('short contact' technique). Specialist nurses may apply intensive treatment with dithranol paste which is covered by stockinette dressings and usually retained overnight. Dithranol should be discontinued if even a low concentration causes acute inflammation; continued use can result in the psoriasis becoming unstable. When applying dithranol, hands should be protected by gloves or they should be washed thoroughly afterwards.

A topical **corticosteroid** (section 13.4) is not generally suitable for long-term use or as the sole treatment of extensive chronic plaque psoriasis; any early improvement is not usually maintained and there is a risk of the condition deteriorating or of precipitating an unstable form of psoriasis e.g. erythrodermic psoriasis or generalised pustular psoriasis on withdrawal. Topical use of potent corticosteroids on widespread psoriasis can also lead to systemic as well as local side-effects. However, topical corticosteroids used short-term may be appropriate to treat psoriasis in specific sites such as the face or flexures with a mild corticosteroid, and psoriasis of the scalp, palms, and soles with a potent corticosteroid. Very potent topical corticosteroids should only be used under specialist supervision.

Combining the use of a corticosteroid with another specific topical treatment may be beneficial in chronic plaque psoriasis; the drugs may be used separately at different times of the day or used together in a single formulation. *Eczema* co-existing with psoriasis may be treated with a corticosteroid, or coal tar, or both.

Phototherapy Phototherapy is available in specialist centres under the supervision of a dermatologist. Narrow band ultraviolet B (UVB) radiation is usually effective for *chronic stable psoriasis* and for *guttate psoriasis*. It can be considered for children with moderately severe psoriasis in whom topical treatment has failed, but it may irritate inflammatory psoriasis. The use of phototherapy and photochemotherapy in children is limited by concerns over carcinogenicity and premature ageing.

Photochemotherapy combining long-wave ultraviolet A radiation with a psoralen (PUVA) is available in specialist centres under the supervision of a dermatologist. The psoralen, which enhances the effect of irradiation, is administered either by mouth or topically. PUVA is effective in most forms of psoriasis, including the *localised palmoplantar pustular psoriasis*. Early adverse effects include phototoxicity and pruritus. Higher cumulative doses exaggerate skin ageing, increase the risk of dysplastic and neoplastic skin lesions especially squamous cancer, and pose a theoretical risk of cataracts.

Phototherapy combined with coal tar, dithranol, topical vitamin D or vitamin D analogues, or oral acitretin, allows reduction of the cumulative dose of phototherapy required to treat psoriasis.

Systemic treatment Systemic treatment is required for severe, resistant, unstable or complicated forms of psoriasis, and it should be initiated only under specialist supervision. Systemic drugs for psoriasis include acitretin and drugs that affect the immune response (section 13.5.3).

Acitretin, a metabolite of etretinate, is a retinoid (vitamin A derivative); it is prescribed by specialists. The main indication of acitretin is severe psoriasis resistant to other forms of therapy. It is also used in disorders of keratinisation such as severe *Darier's disease* (keratosis follicularis), and some forms of *ichthyosis*. Although a minority of cases of psoriasis respond well to acitretin alone, it is only moderately effective in many cases; adverse effects are a limiting factor. A therapeutic effect occurs after 2 to 4 weeks and the maximum benefit after 4 months. Consideration should be given to stopping acitretin if the response is inadequate after 4 months at the optimum dose. Continuous treatment for longer than 6 months is not usually necessary in psoriasis. However, some patients, particularly those with severe ichthyosis, may benefit from longer treatment, provided that the lowest effective dose is used, patients are monitored carefully for adverse effects, and the need for treatment is reviewed regularly. Topical preparations containing keratolytics should normally be stopped before administration of acitretin. Liberal use of emollients should be encouraged and topical corticosteroids can be continued if necessary.

Acitretin is teratogenic; in females of child-bearing age, the possibility of pregnancy must be excluded before treatment and effective contraception must be used during treatment and for at least 3 years afterwards (oral progestogen-only contraceptives not considered effective).

Topical preparations for psoriasis

Vitamin D and analogues

Calcipotriol, **calcitriol**, and **tacalcitol** are used for the management of *plaque psoriasis*. They should be avoided by those with calcium metabolism disorders, and used with caution in *generalised pustular or erythrodermic exfoliative psoriasis* (enhanced risk of hypercalcaemia). Local skin reactions (itching, erythema, burning, paraesthesia, dermatitis) are common. Hands should be washed thoroughly after application to avoid inadvertent transfer to other body areas. Aggravation of psoriasis has also been reported.

CALCIPOTRIOL

Cautions see notes above; avoid use on face; avoid excessive exposure to sunlight and sunlamps

Contra-indications see notes above

Hepatic impairment manufacturers advise avoid in severe impairment

Renal impairment manufacturers advise avoid in severe impairment

Pregnancy manufacturers advise avoid unless essential

Breast-feeding no information available

Side-effects see notes above; also photosensitivity, dry skin; rarely facial or perioral dermatitis

Licensed use Calcipotriol ointment and scalp solution, and *Dovobet*® not licensed for use in children

Indications and dose**Plaque psoriasis**

Child 6–18 years apply ointment twice daily; 6–12 years max. 50 g weekly, over 12 years max. 75 g weekly (less with scalp solution, see below)

Note Patient information leaflet for *Dovonex*® ointment advises liberal application (but note max. recommended weekly dose, above)

Scalp psoriasis (specialist use only)

Child 6–12 years apply scalp solution twice daily; max. 30 mL weekly (less when used with ointment, see below)

Child 12–18 years apply scalp solution twice daily; max. 45 mL weekly (less when used with ointment, see below)

Note When preparations used together max. total calcipotriol 2.5 mg in any one week for child 6–12 years (e.g. scalp solution 20 mL with ointment 30 g); max. 3.75 mg in any one week for child 12–18 years (e.g. scalp solution 30 mL with ointment 45 g)

Calcipotriol (Non-proprietary) (PoM)

Ointment, calcipotriol 50 micrograms/g, net price 120 g = £24.04

Scalp solution, calcipotriol 50 micrograms/mL, net price 60 mL = £42.74, 120 mL = £85.48

Dovonex® (LEO) (PoM)

Ointment, calcipotriol 50 micrograms/g, net price 30 g = £5.78

Excipients include disodium edetate, propylene glycol

With betamethasone

For prescribing information, and for comment on the limited role of corticosteroids in psoriasis, see section 13.4.

Dovobet® (LEO) (PoM)

Ointment, betamethasone (as dipropionate) 0.05%, calcipotriol (as monohydrate) 50 micrograms/g, net price 30 g = £16.54. Label: 28

Excipients include butylated hydroxytoluene

Dose**Stable plaque psoriasis (specialist use only)**

Child 12–18 years apply once daily to max. 30% of body surface for up to 4 weeks; max. 75 g weekly; if necessary, treatment should be continued beyond 4 weeks, or repeated, only on the advice of a specialist

Note When different preparations containing calcipotriol used together, max. total calcipotriol 3.75 mg in any one week for child 12–18 years

Gel, betamethasone (as dipropionate) 0.05%, calcipotriol (as monohydrate) 50 micrograms/g, net price 30 g = £16.54, 60 g = £33.08, 2 × 60 g = £61.43. Label: 28

Excipients include butylated hydroxytoluene

Dose**Scalp psoriasis (specialist use only)**

Child 12–18 years apply 1–4 g to scalp once daily, shampoo off after leaving on scalp overnight or during the day; usual duration of therapy 4 weeks; if necessary, treatment should be continued beyond 4 weeks, or repeated, only on the advice of a specialist

Mild to moderate plaque psoriasis (specialist use only)

Child 12–18 years apply once daily to max. 30% of body surface for up to 4 weeks; max. 75 g weekly; if necessary, treatment should be continued beyond 4 weeks, or repeated, only on the advice of a specialist

Note When different preparations containing calcipotriol used together, max. total calcipotriol 3.75 mg in any one week for child 12–18 years

CALCITRIOL

(1,25-Dihydroxycholecalciferol)

Cautions see notes above

Contra-indications see notes above; do not apply under occlusion

Hepatic impairment manufacturer advises avoid—no information available

Renal impairment manufacturer advises avoid—no information available

Pregnancy manufacturer advises use in restricted amounts only if clearly necessary and to monitor urine- and serum-calcium concentration

Breast-feeding manufacturer advises avoid

Side-effects see notes above

Indications and dose**Mild to moderate plaque psoriasis**

Child 12–18 years apply twice daily; not more than 35% of body surface to be treated daily, max. 30 g daily

Silkis® (Galderma) (PoM)

Ointment, calcitriol 3 micrograms/g, net price 100 g = £16.34

Excipients none as listed in section 13.1.3

TACALCITOL

Cautions see notes above; avoid eyes; monitor serum-calcium concentration if risk of hypercalcaemia; if used in conjunction with UV treatment, UV radiation should be given in the morning and tacalcitol applied at bedtime

Contra-indications see notes above

Renal impairment monitor serum-calcium concentration

Pregnancy manufacturer advises avoid unless no safer alternative—no information available

Breast-feeding manufacturer advises avoid application to breast area; no information available on presence in milk

Side-effects see notes above

Indications and dose**Plaque psoriasis**

Child 12–18 years apply once daily preferably at bedtime; max. 10 g ointment or 10 mL lotion daily

Note When lotion and ointment used together, max. total tacalcitol 280 micrograms in any one week (e.g. lotion 30 mL with ointment 40 g)

Curatoderm® (Almirall) (PoM)

Lotion, tacalcitol (as monohydrate) 4 micrograms/g, net price 30 mL = £12.73

Excipients include disodium edetate, propylene glycol

Ointment, tacalcitol (as monohydrate) 4 micrograms/g, net price 30 g = £13.40, 60 g = £23.14, 100 g = £30.86

Excipients none as listed in section 13.1.3

Tars**TARS**

Cautions application to face and skin flexures; use suitable chemical protection gloves for extemporaneous preparation

Contra-indications not for use in sore, acute, or pustular psoriasis or in presence of infection; avoid

eyes, mucosa, genital or rectal areas; broken or inflamed skin

Side-effects skin irritation and acne-like eruptions, photosensitivity; stains skin, hair, and fabric

Indications and dose

Psoriasis and occasionally chronic atopic eczema

Apply 1–3 times daily starting with low-strength preparations; proprietary preparations, see individual entries below

Note For shampoo preparations see section 13.9

Non-proprietary preparations

May be difficult to obtain. Patients may find newer proprietary preparations more acceptable

Coal Tar Paste, BP

Paste, strong coal tar solution 7.5%, in compound zinc paste

Zinc and Coal Tar Paste, BP

Paste, zinc oxide 6%, coal tar 6%, emulsifying wax 5%, starch 38%, yellow soft paraffin 45%

Excipients include cetostearyl alcohol

Proprietary preparations

Carbo-Dome® (Sandoz)

Cream, coal tar solution 10%, in a water-miscible basis, net price 30 g = £4.77, 100 g = £16.38

Excipients include beeswax, hydroxybenzoates (parabens)

Dose

Psoriasis

Apply to skin 2–3 times daily; product can be diluted with a few drops of freshly boiled and cooled water before applying

Cocoi® (RPH)

Scalp ointment, coal tar solution 12%, salicylic acid 2%, precipitated sulfur 4%, in a coconut oil emollient basis, net price 40 g (with applicator nozzle) = £6.22, 100 g = £11.69

Excipients include cetostearyl alcohol

Dose

Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff

Child 6–12 years medical supervision required

Child 12–18 years apply to scalp once weekly as necessary (if severe use daily for first 3–7 days), shampoo off after 1 hour

Exorex® (Forest)

Lotion, coal tar solution 5% in an emollient basis, net price 100 mL = £8.11, 250 mL = £16.24

Excipients include hydroxybenzoates (parabens)

Dose

Psoriasis

Apply to skin or scalp 2–3 times daily; product can be diluted with a few drops of water before applying

Psoriderm® (Dermal)

Cream, coal tar 6%, lecithin 0.4%, net price 225 mL = £9.42

Excipients include isopropyl palmitate, propylene glycol

Dose

Psoriasis

Apply to skin or scalp 1–2 times daily

Scalp lotion—section 13.9

Sebco® (Derma UK)

Scalp ointment, coal tar solution 12%, salicylic acid 2%, precipitated sulfur 4%, in a coconut oil emollient basis, net price 40 g = £4.54, 100 g = £8.52

Excipients include cetostearyl alcohol

Dose

Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff

Child 6–12 years medical supervision required

Child 12–18 years apply to scalp as necessary (if severe use daily for first 3–7 days), shampoo off after 1 hour

Bath preparations

Coal Tar Solution, BP

Solution, coal tar 20%, polysorbate '80' 5%, in alcohol (96%), net price 500 mL = £11.31. Label: 15

Excipients include polysorbates

Dose

Use 100 mL in an adult-size bath, and proportionally less for a child's bath

Note Strong Coal Tar Solution BP contains coal tar 40%

Polytar Emollient® (Stiefel)

Bath additive, coal tar solution 2.5%, arachis (peanut) oil extract of coal tar 7.5%, tar 7.5%, cade oil 7.5%, light liquid paraffin 35%, net price 500 mL = £5.78

Excipients include isopropyl palmitate

Dose

Psoriasis, eczema, atopic and pruritic dermatoses

Use 2–4 capfuls (15–30 mL) in adult-size bath and proportionally less for a child's bath; soak for 20 minutes

Psoriderm® (Dermal)

Bath emulsion, coal tar 40%, net price 200 mL = £2.74

Excipients include polysorbate 20

Dose

Psoriasis

Use 30 mL in adult-size bath, and proportionally less for a child's bath; soak for 5 minutes

Dithranol

DITHRANOL (Anthralin)

Cautions avoid use near eyes and sensitive areas of skin; see also notes above

Contra-indications hypersensitivity; acute and pustular psoriasis

Pregnancy no adverse effects reported

Breast-feeding no adverse effects reported

Side-effects local burning sensation and irritation; stains skin, hair, and fabrics

Licensed use *Dithrocream*® and *Psorin*® licensed for use in children (age range not specified by manufacturer); *Micanol*® licensed for use in children, but not recommended for infants or young children (age range not specified by manufacturer)

Indications and dose

Subacute and chronic psoriasis

See notes above and under preparations

Note Some of these dithranol preparations also contain coal tar or salicylic acid—for prescribing information see under Tars or under Salicylic Acid

Non-proprietary preparations**1 Dithranol Ointment, BP** (PoM)

Ointment, dithranol, in yellow soft paraffin; usual strengths 0.1–2%. Part of basis may be replaced by hard paraffin if a stiffer preparation is required. Label: 28

Dithranol Paste, BP

Paste, dithranol in zinc and salicylic acid (Lassar's) paste. Usual strengths 0.1–1% of dithranol. Label: 28

Proprietary preparations**Dithrocream®** (Dermal)

Cream, dithranol 0.1%, net price 50 g = £3.77; 0.25%, 50 g = £4.04; 0.5%, 50 g = £4.66; 1%, 50 g = £5.42; (PoM) 2%, 50 g = £6.79. Label: 28

Excipients include cetostearyl alcohol, chlorocresol
Dose

For application to skin or scalp; 0.1–0.5% cream suitable for overnight treatment, 1–2% cream for max. 1 hour

Micano® (GP Pharma)

Cream, dithranol 1% in a lipid-stabilised basis, net price 50 g = £16.18; (PoM) 3%, 50 g = £20.15. Label: 28

Excipients none as listed in section 13.1.3

Dose

For application to skin or scalp, apply 1% cream for up to 30 minutes once daily, if necessary 3% cream can be used under medical supervision

Note At the end of contact time, use plenty of lukewarm (not hot) water to rinse off cream; soap may be used *after* the cream has been rinsed off; use shampoo before applying cream to scalp and if necessary after cream has been rinsed off

Psorin® (LPC)

Ointment, dithranol 0.11%, coal tar 1%, salicylic acid 1.6%, net price 50 g = £9.22, 100 g = £18.44. Label: 28

Excipients include beeswax, wool fat

Dose

For application to skin up to twice daily

Scalp gel, dithranol 0.25%, salicylic acid 1.6% in gel basis containing methyl salicylate, net price 50 g = £7.03. Label: 28

Excipients none as listed in section 13.1.3

Dose

For application to scalp, initially apply on alternate days for 10–20 minutes; may be increased to daily application for max. 1 hour and then wash off

Salicylic acid**SALICYLIC ACID**

For coal tar preparations containing salicylic acid, see under Tars p. 575; for dithranol preparations containing salicylic acid see under Dithranol, above

Cautions see notes above; avoid broken or inflamed skin

Salicylate toxicity Salicylate toxicity may occur particularly if applied on large areas of skin or on neonatal skin

Side-effects sensitivity, excessive drying, irritation, systemic effects after widespread use (see under Cautions)

1. (PoM) if dithranol content more than 1%, otherwise may be sold to the public

Indications and dose

Hyperkeratotic skin disorders see under preparation

Warts and calluses section 13.7

Scalp conditions section 13.9

Fungal nail infections section 13.10.2

Zinc and Salicylic Acid Paste, BP

Paste, (Lassar's Paste), zinc oxide 24%, salicylic acid 2%, starch 24%, white soft paraffin 50%
Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Dose

Child 1 month–18 years apply twice daily

Oral retinoids for psoriasis**ACITRETIN**

Note Acitretin is a metabolite of etretinate

Cautions in children use only in exceptional circumstances (premature epiphyseal closure reported); avoid concomitant use of keratolytics; do not donate blood during and for 2 years after stopping therapy (teratogenic risk); check liver function at start, at least every 4 weeks for first 2 months and then every 3 months; monitor serum-triglyceride and serum-cholesterol concentrations before treatment, 1 month after starting, then every 3 months; diabetes (can alter glucose tolerance—initial frequent blood glucose checks); monitor growth parameters and bone development; investigate atypical musculoskeletal symptoms; avoid excessive exposure to sunlight and unsupervised use of sunlamps; **interactions:** Appendix 1 (retinoids)

Pregnancy prevention In females of child-bearing potential (including those with a history of infertility), exclude pregnancy up to 3 days before treatment, every month during treatment, and every 1–3 months for 3 years after stopping treatment. Treatment should be started on day 2 or 3 of menstrual cycle. Females of child-bearing age must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 3 years after stopping treatment. They should be advised to use at least 1 method of contraception, but ideally they should use 2 methods of contraception. Oral progestogen-only contraceptives are not considered effective. Barrier methods should not be used alone but can be used in conjunction with other contraceptive methods. Each prescription for acitretin should be limited to a supply of up to 30 days' treatment and dispensed within 7 days of the date stated on the prescription. Females of child-bearing age should be advised to seek medical attention immediately if they become pregnant during treatment or within 3 years of stopping treatment. They should be advised to avoid alcohol during treatment and for 2 months after stopping treatment

Contra-indications hyperlipidaemia

Hepatic impairment avoid in severe impairment—risk of further impairment

Renal impairment avoid in severe impairment; increased risk of toxicity

Pregnancy avoid—teratogenic; effective contraception must be used—see Cautions above

Breast-feeding avoid

Side-effects abdominal pain, diarrhoea, nausea, vomiting, dryness and inflammation of mucous membranes, peripheral oedema, reversible increase in serum-cholesterol and serum-triglyceride concentrations (with high doses), headache, arthralgia, myalgia, dryness of conjunctiva (causing conjunctiv-

itis and decreased tolerance to contact lenses), alopecia (reversible on withdrawal), abnormal hair texture, skin exfoliation, pruritus, epidermal fragility, sticky skin, dermatitis, erythema, brittle nails, paronychia; *less commonly* hepatitis, dizziness, visual disturbances, photosensitivity; *rarely* peripheral neuropathy; *very rarely* benign intracranial hypertension (discontinue if severe headache, nausea, vomiting, or visual disturbances occur), bone pain, exostosis (skeletal hyperostosis and extra-osseous calcification reported following long-term treatment with etretinate, and premature epiphyseal closure in children, see Cautions above), night blindness, ulcerative keratitis; *also reported* taste disturbance, rectal haemorrhage, flushing, malaise, drowsiness, granulomatous lesions, impaired hearing, tinnitus, initial worsening of psoriasis, dry skin, sweating

Indications and dose

Harlequin ichthyosis (under expert supervision only)

- By mouth

Neonate 500 micrograms/kg once daily with food or milk (occasionally up to 1 mg/kg daily) with careful monitoring of musculoskeletal development

Severe extensive psoriasis resistant to other forms of therapy, palmoplantar pustular psoriasis, severe congenital ichthyosis, severe Darier's disease (keratosis follicularis) (all under expert supervision only)

- By mouth

Child 1 month–12 years 500 micrograms/kg once daily with food or milk (occasionally up to 1 mg/kg daily) to max. 35 mg daily with careful monitoring of musculoskeletal development (see also p. 574)

Child 12–18 years initially 25–30 mg daily (Darier's disease 10 mg daily) for 2–4 weeks, then adjusted according to response, usual range 25–50 mg daily; up to 75 mg daily for short periods in psoriasis (see also p. 574)

Neotigason® (Actavis) [PoM]

Capsules, acitretin 10 mg (brown/white), net price 60-cap pack = £17.30; 25 mg (brown/yellow), 60-cap pack = £43.00. Label: 10, patient information leaflet, 11, 21

NICE guidance

Tacrolimus and pimecrolimus for atopic eczema (August 2004)

Topical pimecrolimus and tacrolimus are options for atopic eczema not controlled by maximal topical corticosteroid treatment or if there is a risk of important corticosteroid side-effects (particularly skin atrophy).

Topical pimecrolimus is recommended for moderate atopic eczema on the face and neck of children aged 2–16 years and topical tacrolimus is recommended for moderate to severe atopic eczema in children over 2 years. Pimecrolimus and tacrolimus should be used within their licensed indications.

www.nice.org.uk/TA82

The *Scottish Medicines Consortium* (p. 3) has advised (March 2010) that tacrolimus ointment (*Protopic®*) is accepted for restricted use within NHS Scotland for the prevention of flares in children aged over 2 years with moderate to severe atopic eczema in accordance with the licensed indication; initiation of treatment is restricted to doctors (including general practitioners) with a specialist interest and experience in treating atopic eczema with immunomodulatory therapy.

For the role of topical corticosteroids in eczema, see section 13.5.1, and for comment on their limited role in psoriasis, see section 13.4. A systemic corticosteroid (section 6.3.2) such as prednisolone may be used in severe refractory eczema.

Systemic drugs acting on the immune system are generally used by **specialists** in a hospital setting.

Ciclosporin by mouth can be used for *severe psoriasis* and for *severe eczema*. **Azathioprine** (section 8.2.1) or **mycophenolate mofetil** (section 8.2.1) are also used for severe refractory eczema in children.

Methotrexate can be used for *severe resistant psoriasis*; the dose is given **once weekly** and adjusted according to severity of the condition and haematological and biochemical measurements. Folic acid (section 9.1.2) should be given to reduce the possibility of methotrexate toxicity [unlicensed indication]. Folic acid can be given at a dose of 5 mg once weekly on a different day to the methotrexate; alternative regimens may be used in some settings.

Etanercept (a cytokine modulator) is licensed in children over 6 years of age for the treatment of *severe plaque psoriasis* that is inadequately controlled by other systemic treatments and photochemotherapy, or when these other treatments cannot be used because of intolerance or contra-indications.

13.5.3 Drugs affecting the immune response

Drugs affecting the immune response are used for eczema or psoriasis.

Pimecrolimus by topical application is licensed for *mild to moderate atopic eczema*. **Tacrolimus** is licensed for topical use in *moderate to severe atopic eczema*. Both are drugs whose long-term safety is still being evaluated and they should not usually be considered first-line treatment unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Treatment with topical pimecrolimus or topical tacrolimus should be initiated only by prescribers experienced in treating atopic eczema.

CYCLOSPORIN (Cyclosporin)

Cautions section 8.2.2

Additional cautions in atopic dermatitis and psoriasis *Contra-indicated* in abnormal renal function, uncontrolled hypertension (see also below), infections not under control, and malignancy (see also below).

Dermatological and physical examination, including blood pressure and renal function measurements required at least twice before starting. During treatment, monitor serum creatinine every 2 weeks for first 3 months then every month; reduce dose by 25–50% if serum creatinine increases more than 30% above baseline (even if within normal range) and discontinue if reduction not successful within one month. Discontinue if hypertension develops that cannot be controlled by dose reduction or antihypertensive therapy.

Avoid excessive exposure to sunlight and avoid use of UVB or PUVA. *In atopic dermatitis*, also allow herpes simplex infections to clear before starting (if they occur during treatment withdraw if severe); *Staphylococcus aureus* skin infections not absolute contra-indication providing controlled (but avoid erythromycin unless no other alternative—see also **interactions**: Appendix 1 (ciclosporin)); investigate lymphadenopathy that persists despite improvement in atopic dermatitis. *In psoriasis*, also exclude malignancies (including those of skin and cervix) before starting (biopsy any lesions not typical of psoriasis) and treat patients with malignant or pre-malignant conditions of skin only after appropriate treatment (and if no other option); discontinue if lymphoproliferative disorder develops

Hepatic impairment section 8.2.2

Renal impairment see Cautions above

Pregnancy section 8.2.2

Breast-feeding section 8.2.2

Side-effects section 8.2.2

Licensed use not licensed for use in children under 16 years for atopic eczema (dermatitis) or psoriasis

Indications and dose

Short-term treatment (usually max. 8 weeks but may be used for longer under specialist supervision) of severe atopic dermatitis where conventional therapy ineffective or inappropriate

- By mouth, administered in accordance with expert advice

Child 1 month–18 years initially 1.25 mg/kg twice daily, if good initial response not achieved within 2 weeks, increase rapidly to max. 2.5 mg/kg twice daily; initial dose of 2.5 mg/kg twice daily if very severe

Important For preparations and counselling and for advice on conversion between the preparations, see section 8.2.2

Severe psoriasis where conventional therapy ineffective or inappropriate

- By mouth, administered in accordance with expert advice

Child 1 month–18 years initially 1.25 mg/kg twice daily, increased gradually to max. 2.5 mg/kg twice daily if no improvement within 1 month; initial dose of 2.5 mg/kg twice daily justified if condition requires rapid improvement; discontinue if inadequate response after 3 months at the optimum dose; max. duration of treatment usually 1 year unless other treatments cannot be used

Important For preparations and counselling and for advice on conversion between the preparations, see section 8.2.2

Refractory ulcerative colitis section 1.5.3

Transplantation and graft-versus-host disease section 8.2.2

Preparations

Section 8.2.2

METHOTREXATE

Cautions see section 8.1.3; also photosensitivity—psoriasis lesions aggravated by UV radiation (skin ulceration reported)

Contra-indications section 8.1.3

Hepatic impairment avoid—dose-related toxicity

Renal impairment section 8.1.3

Pregnancy section 8.1.3

Breast-feeding section 8.1.3

Side-effects section 8.1.3

Licensed use not licensed for use in children with psoriasis

Indications and dose

Severe uncontrolled psoriasis unresponsive to conventional therapy (specialist use only)

- By mouth

Child 2–18 years initially 200 micrograms/kg (max. 10 mg) once **weekly** increased according to response to 400 micrograms/kg (max. 25 mg) once **weekly**; stop treatment if inadequate response after 3 months at the optimum dose

Safe Practice

Note that the above dose is a **weekly** dose. To avoid error with low-dose methotrexate, it is recommended that:

- the child or their carer is carefully advised of the **dose** and **frequency** and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the child or their carer is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).

Malignant disease section 8.1.3

Rheumatoid arthritis section 10.1.3

Severe Crohn's disease section 1.5.3

Preparations

Section 10.1.3

PIMECROLIMUS

Cautions UV light (avoid excessive exposure to sunlight and sunlamps), avoid other topical treatments except emollients at treatment site; alcohol consumption (risk of facial flushing and skin irritation)

Contra-indications contact with eyes and mucous membranes, application under occlusion, infection at treatment site; congenital epidermal barrier defects; generalised erythroderma; immunodeficiency; concomitant use with drugs that cause immunosuppression (may be prescribed in exceptional circumstances by specialists); application to malignant or potentially malignant skin lesions

Side-effects burning sensation, pruritus, erythema, skin infections (including folliculitis and *less commonly* impetigo, herpes simplex and zoster, molluscum contagiosum); *rarely* papilloma, skin discoloration, local reactions including pain, paraesthesia, peeling, dryness, oedema, and worsening of eczema; skin malignancy reported

Indications and dose

Short-term treatment of mild to moderate atopic eczema (including flares) when topical corticosteroids cannot be used; see also notes above

Child 2–18 years apply twice daily until symptoms resolve (stop treatment if eczema worsens or no response after 6 weeks)

Elidel® (Meda) (PoM)

Cream, pimecrolimus 1%, net price 30 g = £19.69, 60 g = £37.41, 100 g = £59.07. Label: 4, 11, 28

Excipients include benzyl alcohol, cetyl alcohol, propylene glycol, stearyl alcohol

TACROLIMUS

Cautions UV light (avoid excessive exposure to sunlight and sunlamps); alcohol consumption (risk of facial flushing and skin irritation)

Contra-indications infection at treatment site; congenital epidermal barrier defects; generalised erythroderma; immunodeficiency; concomitant use with drugs that cause immunosuppression (may be prescribed in exceptional circumstances by specialists); application to malignant or potentially malignant skin lesions; application under occlusion; avoid contact with eyes and mucous membranes

Pregnancy manufacturer advises avoid unless essential; toxicity in *animal* studies following systemic administration

Breast-feeding manufacturer advises avoid—present in milk following systemic administration

Side-effects application-site reactions including rash, irritation, pain, and paraesthesia; herpes simplex infection, Kaposi's varicelliform eruption; application-site infections; *less commonly* acne; *also reported* rosacea, malignancies (including skin malignancy, cutaneous lymphoma, and other types of lymphomas)

Indications and dose

Short-term treatment of moderate to severe atopic eczema (including flares) either unresponsive to, or in children intolerant of conventional therapy; see also notes above

Child 2–16 years initially apply 0.03% ointment thinly twice daily for up to 3 weeks (consider other treatment if eczema worsens or if no improvement after 2 weeks) then reduce to once daily until lesion clears

Child 16–18 years initially apply 0.1% ointment thinly twice daily until lesion clears (consider other treatment if eczema worsens or if no improvement after 2 weeks); reduce to once daily or switch to 0.03% ointment if clinical condition allows

Prevention of flares in children with moderate to severe atopic eczema and 4 or more flares a year, who have responded to initial treatment with topical tacrolimus

Child 2–16 years apply 0.03% ointment thinly twice weekly (with an interval of 2–3 days between applications); use short-term treatment regimen during an acute flare; interrupt preventative therapy after 1 year to reassess condition

Child 16–18 years apply 0.1% ointment thinly twice weekly (with an interval of 2–3 days between applications); use short-term treatment regimen during an acute flare; review need for preventative therapy after 1 year

Other indications section 8.2.2

Protopic® (Astellas) (PoM)

Ointment, tacrolimus (as monohydrate) 0.03%, net price 30 g = £19.44, 60 g = £35.46; 0.1%, 30 g = £21.60, 60 g = £39.40. Label: 4, 11, 28

Excipients include beeswax

Cytokine modulators

ETANERCEPT

Cautions section 10.1.3, p. 516

Important See section 10.1.3, p. 516 for information on tuberculosis and blood disorders

Contra-indications section 10.1.3, p. 516

Hepatic impairment section 10.1.3, p. 516

Pregnancy section 10.1.3, p. 516

Breast-feeding section 10.1.3, p. 516

Side-effects section 10.1.3, p. 516

Indications and dose

Severe plaque psoriasis

- By subcutaneous injection

Child 6–18 years 800 micrograms/kg (max. 50 mg) once weekly for up to 24 weeks; discontinue if no response after 12 weeks

Polyarticular-course juvenile idiopathic arthritis

section 10.1.3

Preparations

Section 10.1.3

13.6 Acne and rosacea

13.6.1 Topical preparations for acne

13.6.2 Oral preparations for acne

Acne vulgaris Acne vulgaris commonly affects children around puberty and occasionally affects infants. Treatment of acne should be commenced early to prevent scarring; lesions may worsen before improving. The choice of treatment depends on age, severity, and whether the acne is predominantly inflammatory or comedonal.

Mild to moderate acne is generally treated with topical preparations, such as benzoyl peroxide, azelaic acid, and retinoids (section 13.6.1).

For *moderate to severe inflammatory acne* or where topical preparations are not tolerated or are ineffective or where application to the site is difficult, systemic treatment (section 13.6.2) with oral antibacterials may be effective. **Co-cyprindiol** (cyproterone acetate with ethinylestradiol) has anti-androgenic properties and may be useful in young women with acne refractory to other treatments.

Severe acne, acne unresponsive to prolonged courses of oral antibacterials, acne with scarring, or acne associated with psychological problems calls for early referral to a consultant dermatologist who may prescribe oral isotretinoin (section 13.6.2).

Neonatal and infantile acne Inflammatory papules, pustules, and occasionally comedones may develop at birth or within the first month; most neonates with acne do not require treatment. Acne developing at 3–6 months of age may be more severe and persistent; lesions are usually confined to the face. Topical preparations containing benzoyl peroxide (at the lowest strength possible to avoid irritation), adapalene, or tretinoin may be used if treatment for infantile acne is necessary. In infants with inflammatory acne, oral **erythromycin** (section 5.1.5) is used because topical preparations for acne are not well tolerated. In cases of

erythromycin-resistant acne, oral isotretinoin (section 13.6.2) can be given on the advice of a consultant dermatologist.

Rosacea The adult form of rosacea rarely occurs in children. Persistent or repeated use of potent topical corticosteroids may cause periorificial rosacea (steroid acne). The pustules and papules of rosacea may be treated for at least 6 weeks with a topical **metronidazole** preparation (section 13.10.1.2), or a systemic antibacterial such as **erythromycin** (section 5.1.5), or for a child over 12 years, **oxytetracycline** (section 5.1.3). Tetracyclines are **contra-indicated** in children under 12 years of age.

13.6.1 Topical preparations for acne

In mild to moderate acne, comedones and inflamed lesions respond well to benzoyl peroxide (see below) or topical retinoids (see p. 582). Alternatively, topical application of an antibacterial such as erythromycin or clindamycin may be effective for inflammatory acne. However, topical antibacterials are probably no more effective than benzoyl peroxide and may promote the emergence of resistant organisms. If topical preparations prove inadequate, oral preparations may be needed (section 13.6.2). The choice of product and formulation (gel, solution, lotion, or cream) is largely determined by skin type, patient preference, and previous usage of acne products.

Benzoyl peroxide and azelaic acid

Benzoyl peroxide is effective in mild to moderate acne. Both comedones and inflamed lesions respond well to benzoyl peroxide. The lower concentrations seem to be as effective as higher concentrations in reducing inflammation. It is usual to start with a lower strength and to increase the concentration of benzoyl peroxide gradually. The usefulness of benzoyl peroxide washes is limited by the short time the products are in contact with the skin. Adverse effects include local skin irritation, particularly when therapy is initiated, but the scaling and redness often subside with a reduction in benzoyl peroxide concentration, frequency, and area of application. If the acne does not respond after 2 months then use of a topical antibacterial should be considered.

Azelaic acid has antimicrobial and comedonal properties. It may be used as an alternative to benzoyl peroxide or to a topical retinoid for treating mild to moderate comedonal acne, particularly of the face; azelaic acid is less likely to cause local irritation than benzoyl peroxide.

BENZOYL PEROXIDE

Cautions avoid contact with eyes, mouth, mucous membranes, and broken skin; may bleach fabrics and hair; avoid excessive exposure to sunlight

Side-effects skin irritation (reduce frequency or suspend use until irritation subsides and re-introduce at reduced frequency)

Licensed use **Quinoderm**® is licensed for use in children; *all other preparations*, not licensed for use in treatment of infantile acne

Indications and dose

Acne vulgaris

Child 12–18 years apply 1–2 times daily preferably after washing with soap and water, start treatment with lower-strength preparations

Note May bleach clothing

Infantile acne

Child 1 month–2 years apply 1–2 times daily; start treatment with lower-strength preparations

Acnecide® (Galderma)

Gel, benzoyl peroxide 5% in an aqueous gel basis, net price 30 g = £5.44, 60 g = £12.56

Excipients include propylene glycol

Brevoxyl® (GSK)

Cream, benzoyl peroxide 4% in an aqueous basis, net price 50 g = £4.13

Excipients include cetyl alcohol, fragrance, stearyl alcohol

PanOxyl® (GSK)

Aquagel (= aqueous gel), benzoyl peroxide 2.5%, net price 40 g = £1.76; 5%, 40 g = £1.92; 10%, 40 g = £2.13

Excipients include propylene glycol

Cream, benzoyl peroxide 5% in a non-greasy basis, net price 40 g = £1.89

Excipients include isopropyl palmitate, propylene glycol

Gel, benzoyl peroxide 10% in an aqueous alcoholic basis, net price 40 g = £1.99

Excipients include fragrance

Note May be difficult to obtain

With antimicrobials

See also Topical Antibacterials for Acne, p. 582 and Antibacterials, p. 582

Duac® Once Daily (GSK) (PoM)

Gel, benzoyl peroxide 3%, clindamycin 1% (as phosphate) in an aqueous basis, net price 30 g = £11.94

Excipients include disodium edetate

Dose

Acne vulgaris

Child 12–18 years apply once daily in the evening

Gel, benzoyl peroxide 5%, clindamycin 1% (as phosphate) in an aqueous basis, net price 25 g = £9.95, 50 g = £19.90

Excipients include disodium edetate

Dose

Acne vulgaris

Child 12–18 years apply once daily in the evening

Quinoderm® (Alliance)

Cream, benzoyl peroxide 5%, potassium hydroxy-quinoline sulfate 0.5%, in an astringent vanishing-cream basis, net price 50 g = £2.43

Excipients include cetostearyl alcohol, edetic acid (EDTA)

Cream, benzoyl peroxide 10%, potassium hydroxy-quinoline sulfate 0.5%, in an astringent vanishing-cream basis, net price 25 g = £1.58, 50 g = £2.55

Excipients include cetostearyl alcohol, edetic acid (EDTA)

Dose

Acne vulgaris, acneform eruptions, folliculitis

Apply 2–3 times daily

AZELAIC ACID

Cautions avoid contact with eyes, mouth, and mucous membranes

Side-effects local irritation (reduce frequency or discontinue temporarily); *less commonly* skin discoloration; *also reported* worsening of asthma

Indications and dose

See under preparations

Finacea® (Bayer) (PoM)

Gel, azelaic acid 15%, net price 30 g = £7.48

Excipients include disodium edetate, polysorbate 80, propylene glycol

Dose

Facial acne vulgaris

Child 12–18 years apply twice daily; discontinue if no improvement after 1 month

Skinoren® (Bayer) (PoM)

Cream, azelaic acid 20%, net price 30 g = £3.74

Excipients include propylene glycol

Dose

Acne vulgaris

Child 12–18 years apply twice daily (sensitive skin, once daily for first week)

Topical antibacterials for acne

In the treatment of mild to moderate inflammatory acne, topical antibacterials may be no more effective than topical benzoyl peroxide or tretinoin. Topical antibacterials are probably best reserved for children who wish to avoid oral antibacterials or who cannot tolerate them.

Typical preparations of **erythromycin** and **clindamycin** may be used to treat *inflamed lesions* in mild to moderate acne when topical benzoyl peroxide or tretinoin is ineffective or poorly tolerated. Topical benzoyl peroxide, azelaic acid, or retinoids used in combination with an antibacterial (topical or systemic) may be more effective than an antibacterial used alone. Topical antibacterials can produce mild irritation of the skin, and on rare occasions cause sensitisation; gastro-intestinal disturbances have been reported with topical clindamycin. Antibacterial resistance of *Propionibacterium acnes* is increasing; there is cross-resistance between erythromycin and clindamycin. To avoid development of resistance:

- when possible use non-antibiotic antimicrobials (such as benzoyl peroxide or azelaic acid);
- avoid concomitant treatment with different oral and topical antibacterials;
- if a particular antibacterial is effective, use it for repeat courses if needed (short intervening courses of benzoyl peroxide or azelaic acid may eliminate any resistant *propionibacteria*);
- do not continue treatment for longer than necessary (but treatment with a topical preparation should be continued for at least 6 months).

ANTIBACTERIALS

Cautions some manufacturers advise preparations containing alcohol are not suitable for use with benzoyl peroxide; discontinue clindamycin preparations immediately if diarrhoea or colitis occur

Indications and dose

Acne vulgaris for dose, see under preparations

Dalacin T® (Pharmacia) (PoM)

Topical solution, clindamycin 1% (as phosphate), in an aqueous alcoholic basis, net price (both with applicator) 30 mL = £4.34, 50 mL = £7.23

Excipients include propylene glycol

Dose

Apply thinly twice daily

Lotion, clindamycin 1% (as phosphate) in an aqueous basis, net price 30 mL = £5.08, 60 mL = £10.16

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Dose

Apply thinly twice daily

Stiemycin® (Stiefel) (PoM)

Solution, erythromycin 2% in an alcoholic basis, net price 50 mL = £7.69

Excipients include propylene glycol

Dose

Child 12–18 years apply thinly twice daily

Zindaclin® (Crawford) (PoM)

Gel, clindamycin 1% (as phosphate), net price 30 g = £8.66

Excipients include propylene glycol

Dose

Child 12–18 years apply thinly once daily

Zineryt® (Astellas) (PoM)

Topical solution, powder for reconstitution, erythromycin 40 mg, zinc acetate 12 mg/mL when reconstituted with solvent containing ethanol, net price per pack of powder and solvent to provide 30 mL = £7.71, 90 mL = £16.68

Excipients none as listed in section 13.1.3

Dose

Apply twice daily

Topical retinoids and related preparations for acne

Topical **tretinoin**, its isomer **isotretinoin**, and **adapalene** (a retinoid-like drug), are useful for treating comedones and inflammatory lesions in mild to moderate acne. Patients should be warned that some redness and skin peeling can occur initially but settles with time. If undue irritation occurs, the frequency of application should be reduced or treatment suspended until the reaction subsides; if irritation persists, discontinue treatment. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop.

Tretinoin can be used under specialist supervision to treat infantile acne; adapalene can also be used. See also Neonatal and Infantile Acne, p. 580.

Cautions Topical retinoids should be avoided in severe acne involving large areas. Contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin should be avoided. Topical retinoids should be used with caution on sensitive areas such as the neck, and accumulation in angles of the nose should be avoided. Exposure to UV light (including sunlight, solariums) should be avoided; if sun exposure is unavoidable, an appropriate sunscreen (section 13.8.1) or protective clothing should be used. Use of retinoids with abrasive cleaners, comedogenic or astringent cosmetics should be avoided. Allow peeling (result-

ing from other irritant treatments) to subside before using a topical retinoid; alternating a preparation that causes peeling with a topical retinoid may give rise to contact dermatitis (reduce frequency of retinoid application).

Pregnancy Topical retinoids are contra-indicated in pregnancy; females of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered effective).

Side-effects Local reactions include burning, erythema, stinging, pruritus, dry or peeling skin (discontinue if severe). Increased sensitivity to UVB light or sunlight occurs. Temporary changes of skin pigmentation with tretinoin have been reported. Eye irritation and oedema, and blistering or crusting of skin have been reported rarely.

ADAPALENE

Cautions see notes above

Pregnancy see notes above

Breast-feeding amount of drug in milk probably too small to be harmful; ensure infant does not come in contact with treated areas

Side-effects see notes above

Licensed use not licensed for use in infantile acne

Indications and dose

Infantile acne

Child 1 month–2 years apply thinly once daily in the evening

Mild to moderate acne vulgaris

Child 12–18 years apply thinly once daily in the evening

Differin® (Galderma) (PoM)

Cream, adapalene 0.1%, net price 45 g = £16.15.

Label: 11

Excipients include disodium edetate, hydroxybenzoates (parabens)

Gel, adapalene 0.1%, net price 45 g = £16.15. **Label:** 11

Excipients include disodium edetate, hydroxybenzoates (parabens), propylene glycol

With benzoyl peroxide

Epiduo® (Galderma) (PoM)

Gel, adapalene 0.1%, benzoyl peroxide 2.5%, net price 45 g = £17.91. **Label:** 11

Excipients include disodium edetate, polysorbate 80, propylene glycol

Dose

Acne vulgaris

Child 9–18 years apply thinly once daily in the evening

Note May bleach clothing and hair

Note The *Scottish Medicines Consortium* (p. 3) has advised (March 2014) that *Epiduo®* should be restricted for use in mild to moderate facial acne when monotherapy with benzoyl peroxide or adapalene is inappropriate

ISOTRETINOIN

Note Isotretinoin is an isomer of tretinoin

Important For prescribing information on isotretinoin when given by mouth, see p. 585

Cautions (*topical application only*) see notes above; also personal or familial history of non-melanoma skin cancer

Contra-indications (*topical application only*) rosacea; perioral dermatitis

Pregnancy (*topical application only*) see notes above

Breast-feeding avoid

Side-effects (*topical application only*) see notes above

Indications and dose

Acne vulgaris

Apply thinly 1–2 times daily

Isotrex® (Stiefel) (PoM)

Gel, isotretinoin 0.05%, net price 30 g = £5.94.

Label: 11

Excipients include butylated hydroxytoluene

With antibacterial

Isotrexin® (Stiefel) (PoM)

Gel, isotretinoin 0.05%, erythromycin 2% in ethanolic basis, net price 30 g = £7.47. **Label:** 11

Excipients include butylated hydroxytoluene

TRETINOIN

Note Tretinoin is the acid form of vitamin A

Cautions see notes above

Contra-indications personal or familial history of non-melanoma skin cancer; rosacea; perioral dermatitis

Pregnancy see notes above

Breast-feeding amount of drug in milk after topical application probably too small to be harmful; ensure infant does not come into contact with treated areas

Side-effects see notes above

Indications and dose

See under preparations

Malignant disease section 8.1.5

With antibacterial

Aknemycin Plus® (Almirall) (PoM)

Solution, tretinoin 0.025%, erythromycin 4% in an alcoholic basis, net price 25 mL = £7.05. **Label:** 11

Excipients none as listed in section 13.1.3

Dose

Acne (all forms), particularly that associated with oily skin

Apply thinly 1–2 times daily

Other topical preparations for acne

A topical preparation of **nicotinamide** is available for inflammatory acne.

NICOTINAMIDE

Cautions avoid contact with eyes and mucous membranes (including nose and mouth); reduce frequency of application if excessive dryness, irritation, or peeling

Side-effects dry skin, pruritus, erythema, burning, irritation

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Inflammatory acne vulgaris see under preparations below

Nicam® (Dermal)

Gel, nicotinamide 4%, net price 60 g = £7.10

Excipients none as listed in section 13.1.3**Dose**

Apply twice daily; reduce to once daily or on alternate days if irritation occurs

13.6.2 Oral preparations for acne**Oral antibacterials for acne**

Oral antibacterials may be used in *moderate to severe inflammatory acne* when topical treatment is not adequately effective or is inappropriate. Concomitant anti-comedonal treatment with topical benzoyl peroxide or azelaic acid may also be required (section 13.6.1).

Tetracyclines should not be given to children under 12 years. In children over 12 years, either **oxytetracycline** or **tetracycline** (section 5.1.3) is usually given for acne in a dose of 500 mg twice daily. If there is no improvement after the first 3 months another oral antibacterial should be used. Maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer.

Doxycycline and **lymecycline** (section 5.1.3) are alternatives to tetracycline in children over 12 years. Doxycycline can be used in a dose of 100 mg daily. Lyme cycline is given in a dose of 408 mg daily.

Although **minocycline** is as effective as other tetracyclines for acne, it is associated with a greater risk of lupus erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation; it is given in a dose of 100 mg once daily or 50 mg twice daily.

Erythromycin (section 5.1.5) in a dose of 500 mg twice daily for children over 12 years is an alternative for the management of moderate to severe acne with inflamed lesions, but propionibacteria strains resistant to erythromycin are becoming widespread and this may explain poor response. Infants with acne requiring oral treatment with erythromycin should be given 250 mg once daily or 125 mg twice daily; in cases of erythromycin-resistant *P. acnes* in infants, oral isotretinoin may be used on the advice of a consultant dermatologist.

Concomitant use of different topical and systemic antibacterials is undesirable owing to the increased likelihood of the development of bacterial resistance.

Hormone treatment for acne

Co-cyprindiol (cyproterone acetate with ethinylestradiol) contains an anti-androgen. It is no more effective than an oral broad-spectrum antibacterial but is useful in females of childbearing age who also wish to receive oral contraception.

Improvement of acne with co-cyprindiol probably occurs because of decreased sebum secretion which is under androgen control. Some females with moderately severe hirsutism may also benefit because hair growth is also androgen-dependent.

There is an increased risk of venous thromboembolism in women taking co-cyprindiol, particularly during the first year of use. The incidence of venous thromboembolism is 1.5–2 times higher in women using co-cyprindiol than in women using combined oral contraceptives containing levonorgestrel, but the risk may be similar to that associated with combined oral contraceptives containing third-generation progestogens (desogestrel or gestodene) or drospirenone (see section 7.3.1). Co-cyprindiol is licensed for use in women with moderate to severe acne that has not responded to topical therapy or oral antibacterials, and for moderately severe hirsutism; it should not be used solely for contraception. It is contra-indicated in those with a history of venous or arterial thromboembolism, or in those with severe or multiple risk factors for arterial disease or venous thromboembolism (see section 7.3.1). Women requiring co-cyprindiol may have an inherently increased risk of cardiovascular disease.

CO-CYPRINDIOL

A mixture of cyproterone acetate and ethinylestradiol in the mass proportions 2000 parts to 35 parts, respectively

Cautions see under Combined Hormonal Contraceptives, section 7.3.1

Contra-indications see under Combined Hormonal Contraceptives, section 7.3.1

Hepatic impairment see under Combined Hormonal Contraceptives, section 7.3.1

Pregnancy avoid—risk of feminisation of male fetus with cyproterone

Breast-feeding manufacturer advises avoid; possibility of anti-androgen effects in neonate with cyproterone

Side-effects see under Combined Hormonal Contraceptives, section 7.3.1

Licensed use licensed for use in females of child-bearing age

Indications and dose

Moderate to severe acne in females of child-bearing age refractory to topical therapy or oral antibacterials (but see notes above), moderately severe hirsutism

- **By mouth**

1 tablet daily for 21 days starting on day 1 of menstrual cycle; subsequent cycles repeated after a 7-day interval (during which withdrawal bleeding occurs); time to symptom remission, at least 3 months; review need for treatment regularly

Co-cyprindiol (Non-proprietary) ▼ **[PoM]**

Tablets, co-cyprindiol 2000/35 (cyproterone acetate 2 mg, ethinylestradiol 35 micrograms), net price 63-tab pack = £5.40

Brands include Acnacin®, Cicafem®, Clairette®

Dianette® (Bayer) ▼ **[PoM]**

Tablets, beige, s/c, co-cyprindiol 2000/35 (cyproterone acetate 2 mg, ethinylestradiol 35 micrograms), net price 63-tab pack = £7.71

Oral retinoid for acne

The retinoid **isotretinoin** reduces sebum secretion. It is used for the systemic treatment of nodulo-cystic and conglobate acne, severe acne, acne with scarring, or for

acne which has not responded to an adequate course of a systemic antibacterial. Isotretinoin is used for the treatment of severe infantile acne resistant to erythromycin.

Isotretinoin is a toxic drug that should be prescribed **only** by, or under the supervision of, a consultant dermatologist. It is given for at least 16 weeks; repeat courses are not normally required.

Side-effects of isotretinoin include severe dryness of the skin and mucous membranes, nose bleeds, and joint pains. The drug is **teratogenic** and must **not** be given to females of child-bearing age unless they practise effective contraception (oral progestogen-only contraceptives not considered effective) and then only after detailed assessment and explanation by the physician. They must also be registered with a pregnancy prevention programme (see under Cautions below).

Although a causal link between isotretinoin use and psychiatric changes (including suicidal ideation) has not been established, the possibility should be considered before initiating treatment; if psychiatric changes occur during treatment, isotretinoin should be stopped, the prescriber informed, and specialist psychiatric advice should be sought.

ISOTRETINOIN

Note Isotretinoin is an isomer of tretinoin

Cautions see notes above; also avoid blood donation during treatment and for at least 1 month after treatment; history of depression; monitor all patients for depression; measure hepatic function and serum lipids before treatment, 1 month after starting and then every 3 months (reduce dose or discontinue if transaminase or serum lipids persistently raised); discontinue if uncontrolled hypertriglyceridaemia or pancreatitis; diabetes; dry eye syndrome (associated with risk of keratitis); avoid keratolytics; **interactions:** Appendix 1 (retinoids)

Pregnancy prevention In women of child-bearing potential, exclude pregnancy up to 3 days before treatment (start treatment on day 2 or 3 of menstrual cycle), every month during treatment (unless there are compelling reasons to indicate that there is no risk of pregnancy), and 5 weeks after stopping treatment—perform pregnancy test in the first 3 days of the menstrual cycle. Women must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after stopping treatment. Women should be advised to use at least 1 method of contraception, but ideally they should use 2 methods of contraception. Oral progestogen-only contraceptives are not considered effective. Barrier methods should not be used alone, but can be used in conjunction with other contraceptive methods. Each prescription for isotretinoin should be limited to a supply of up to 30 days' treatment and dispensed within 7 days of the date stated on the prescription; repeat prescriptions or faxed prescriptions are not acceptable. Women should be advised to discontinue treatment and to seek prompt medical attention if they become pregnant during treatment or within 1 month of stopping treatment.

Counselling Warn patient to avoid wax epilation (risk of epidermal stripping), dermabrasion, and laser skin treatments (risk of scarring) during treatment and for at least 6 months after stopping; patient should avoid exposure to UV light (including sunlight) and use sunscreen and emollient (including lip balm) preparations from the start of treatment

Contra-indications hypervitaminosis A, hyperlipidaemia

Hepatic impairment avoid—further impairment may occur

Renal impairment in severe impairment, reduce initial dose and increase gradually, if necessary, up to 1 mg/kg daily as tolerated

Pregnancy avoid—teratogenic; effective contraception must be used—see Pregnancy Prevention above

Breast-feeding avoid

Side-effects dryness of skin (with dermatitis, scaling, thinning, erythema, pruritus), epidermal fragility (trauma may cause blistering), dryness of lips (sometimes cheilitis), dryness of eyes (with blepharitis and conjunctivitis), dryness of pharyngeal mucosa (with hoarseness), dryness of nasal mucosa (with epistaxis), headache, myalgia and arthralgia, raised plasma-triglyceride concentration (risk of pancreatitis if triglycerides above 9 mmol/litre), raised serum-cholesterol concentration (with reduced high-density lipoprotein concentration), raised blood-glucose concentration, raised serum-transaminase concentration, haematuria and proteinuria, thrombocytopenia, thrombocytosis, neutropenia and anaemia; *rarely* mood changes (depression, aggressive behaviour, anxiety, and very rarely psychosis and suicidal ideation)—expert referral required, skin reactions (including reports of Stevens-Johnson syndrome and toxic epidermal necrolysis), alopecia; *very rarely* nausea, hepatitis, inflammatory bowel disease, gastrointestinal haemorrhage, haemorrhagic diarrhoea (discontinue treatment), benign intracranial hypertension (avoid concomitant tetracyclines), convulsions, malaise, drowsiness, dizziness, diabetes mellitus, lymphadenopathy, hyperuricaemia, glomerulonephritis, tendonitis, arthritis, raised serum-creatinine kinase concentration, bone changes (including reduced bone density, early epiphyseal closure, and skeletal hyperostosis) and calcification of tendons and ligaments following long-term administration, visual disturbances (papilloedema, corneal opacities, cataracts, decreased night vision, photophobia, blurred vision, colour blindness)—expert referral required and consider withdrawal, decreased tolerance to contact lenses, keratitis, impaired hearing, Gram-positive infections of skin and mucous membranes, exacerbation of acne, acne fulminans, allergic vasculitis and granulomatous lesions, paronychia, hirsutism, nail dystrophy, skin hyperpigmentation, photosensitivity, increased sweating

Licensed use not licensed for use in infantile acne

Indications and dose

Acne vulgaris under supervision of consultant dermatologist, see notes above

• By mouth

Child 12–18 years 500 micrograms/kg daily (in 1–2 divided doses), increased if necessary to 1 mg/kg daily, for 16–24 weeks (repeat treatment course after a period of at least 8 weeks if relapse after first course); max. cumulative dose 150 mg/kg per course

Severe infantile acne under supervision of a consultant dermatologist, see p. 580

• By mouth

Child 1 month–2 years 200 micrograms/kg daily (in 1–2 divided doses), increased if necessary to 1 mg/kg daily, for 16–24 weeks; max. cumulative dose 150 mg/kg per course

Isotretinoin (Non-proprietary) [PoM]

Capsules, isotretinoin 5 mg, net price 56-cap pack = £14.78; 20 mg, 56-cap pack = £37.85. Label: 10, patient information leaflet, 11, 21

Rocaccutane® (Roche) [PoM]

Capsules, isotretinoin 10 mg (brown-red), net price 30-cap pack = £14.54; 20 mg (brown-red/white), 30-cap pack = £20.02. Label: 10, patient information card, 11, 21

13.7 Preparations for warts and calluses

Warts (verruca vulgaris) are common, benign, self-limiting, and usually asymptomatic. They are caused by a human papillomavirus, which most frequently affects the hands, feet (plantar warts), and the anogenital region (see below); treatment usually relies on local tissue destruction and is required only if the warts are painful, unsightly, persistent, or cause distress. In immunocompromised children, warts may be more difficult to eradicate.

Preparations of **salicylic acid**, **formaldehyde**, **glutaraldehyde** or **silver nitrate** are used for the removal of warts on hands and feet. **Salicylic acid** is a useful keratolytic which may be considered first-line in the treatment of warts; it is also suitable for the removal of *corns* and *calluses*. Preparations of salicylic acid in a collodion basis are available but some children may develop an allergy to colophony in the formulation; collodion should be avoided in children allergic to elastic adhesive plaster. Cryotherapy causes pain, swelling, and blistering, and may be no more effective than topical salicylic acid in the treatment of warts.

SALICYLIC ACID

Cautions significant peripheral neuropathy, patients with diabetes at risk of neuropathic ulcers; impaired peripheral circulation; protect surrounding skin and avoid broken skin; not suitable for application to face, anogenital region, or large areas

Side-effects skin irritation, skin ulceration (with high concentrations)

Licensed use not licensed for use in children under 2 years

Indications and dose**Warts on hands and feet (plantar)**

For dose see preparations; apply carefully to wart and protect surrounding skin (e.g. with soft paraffin or specially designed plaster); rub wart surface gently with file or pumice stone once weekly; treatment may need to be continued for up to 3 months

Psoriasis section 13.5.2

Fungal nail infections section 13.10.2

Cuplex® (Crawford)

Gel, salicylic acid 11%, lactic acid 4%, in a collodion basis, net price 5 g = £2.88. Label: 15

Dose

Apply twice daily

Note Contains colophony (see notes above)

Duofilm® (GSK)

Paint, salicylic acid 16.7%, lactic acid 16.7%, in flexible collodion, net price 15 mL (with applicator) = £2.25. Label: 15

Dose

Apply daily

Occlusal® (Alliance)

Cutaneous solution, salicylic acid 26% in polyacrylic solution, net price 10 mL (with applicator) = £3.56.

Label: 15

Dose

Apply daily

Salactol® (Dermal)

Paint, salicylic acid 16.7%, lactic acid 16.7%, in flexible collodion, net price 10 mL (with applicator) = £1.71. Label: 15

Dose

Apply daily

Note Contains colophony (see notes above)

Salatac® (Dermal)

Gel, salicylic acid 12%, lactic acid 4% in a collodion basis, net price 8 g (with applicator) = £2.98. Label: 15

Dose

Apply daily

Verrugon® (Ransom)

Ointment, salicylic acid 50% in a paraffin basis, net price 6 g = £3.12

Dose

Apply daily

FORMALDEHYDE

Cautions see under Salicylic Acid

Side-effects see under Salicylic Acid

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Warts, particularly plantar warts for dose see preparation below

Veracur® (Typharm)

Gel, formaldehyde 0.75% in a water-miscible gel basis, net price 15 g = £2.41

Dose

Apply twice daily

GLUTARALDEHYDE

Cautions protect surrounding skin; not for application to face, mucosa, or anogenital areas

Side-effects rashes, skin irritation (discontinue if severe); stains skin brown

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Warts, particularly plantar warts

Apply twice daily

Glutarol® (Dermal)

Solution (= application), glutaraldehyde 10%, net price 10 mL (with applicator) = £2.07

SILVER NITRATE

Cautions protect surrounding skin and avoid broken skin; not suitable for application to face, ano-genital region, or large areas

Side-effects chemical burns on surrounding skin; stains skin and fabric

Licensed use no age range specified by manufacturer

Indications and dose**Common warts and verrucas**

Apply moistened caustic pencil tip for 1–2 minutes; repeat after 24 hours up to max. 3 applications for warts or max. 6 applications for verrucas. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application.

Umbilical granulomas

Apply moistened caustic pencil tip (usually containing silver nitrate 40%) for 1–2 minutes while protecting surrounding skin with soft paraffin.

AVOCA® (Bray)

Caustic pencil, tip containing silver nitrate 40%, potassium nitrate 60%, net price = £0.94; silver nitrate 95%, potassium nitrate 5%, treatment pack (including emery file, 6 adhesive dressings and protector pads) = £2.27

Anogenital warts

Anogenital warts (condylomata acuminata) in children are often asymptomatic and require only a simple barrier preparation. If treatment is required it should be supervised by a hospital specialist. Persistent warts on genital skin may require treatment with cryotherapy or other forms of physical ablation under general anaesthesia.

Podophyllotoxin (the major active ingredient of podophyllum), or **imiquimod** are used to treat external anogenital warts; these preparations can cause considerable irritation of the treated area and are therefore suitable only for children who are able to cooperate with the treatment.

IMIQUIMOD

Cautions avoid normal or broken skin and open wounds; not suitable for internal genital warts; uncircumcised males (risk of phimosis or stricture of foreskin); autoimmune disease; immunosuppressed patients

Pregnancy no evidence of teratogenicity or toxicity in animal studies; manufacturer advises caution

Breast-feeding no information available

Side-effects local reactions (including itching, burning sensation, erythema, erosion, oedema, excoriation, and scabbing); headache; influenza-like symptoms; myalgia; *less commonly* local ulceration and alopecia; *rarely* Stevens-Johnson syndrome and cutaneous lupus erythematosus-like effect; *very rarely* dysuria in females; permanent hypopigmentation or hyperpigmentation reported

Licensed use not licensed for use in children

Indications and dose

External genital and perianal warts (for use under specialist supervision only)

Apply thinly 3 times a week at night until lesions resolve (max. 16 weeks)

Important Should be rubbed in and allowed to stay on the treated area for 6–10 hours then washed off with mild soap and water (uncircumcised males treating warts under foreskin should wash the area daily). The cream should be washed off before sexual contact

Aldara® (Meda) (PoM)

Cream, imiquimod 5%, net price 12-sachet pack = £48.60. Label: 10, patient information leaflet

Excipients include benzyl alcohol, cetyl alcohol, hydroxybenzoates (parabens), polysorbate 60, stearyl alcohol

Condoms may damage latex condoms and diaphragms

PODOPHYLLOTOXIN

Cautions see notes above; avoid normal skin and open wounds; keep away from face; very irritant to eyes

Pregnancy avoid

Breast-feeding avoid

Side-effects local irritation

Licensed use not licensed for use in children

Indications and dose

See under preparations (for use under specialist supervision only)

Condylone® (Takeda) (PoM)

Solution, podophyllotoxin 0.5% in alcoholic basis, net price 3.5 mL (with applicators) = £14.49. Label: 15

Dose

Condylomata acuminata affecting the penis or the female external genitalia

Child 2–18 years (see notes above) apply twice daily for 3 consecutive days; treatment may be repeated at weekly intervals if necessary for a total of five 3-day treatment courses; direct medical supervision for lesions in the female and for lesions greater than 4 cm² in the male; max. 50 single applications ('loops') per session (consult product literature)

Warticon® (GSK) (PoM)

Cream, podophyllotoxin 0.15%, net price 5 g (with mirror) = £14.86

Excipients include butylated hydroxyanisole, cetyl alcohol, hydroxybenzoates (parabens), sorbic acid, stearyl alcohol

Dose

Condylomata acuminata affecting the penis or the female external genitalia

Child 2–18 years (see notes above) apply twice daily for 3 consecutive days; treatment may be repeated at weekly intervals if necessary for a total of four 3-day treatment courses; direct medical supervision for lesions greater than 4 cm²

Solution, blue, podophyllotoxin 0.5% in alcoholic basis, net price 3 mL (with applicators) = £12.38.

Label: 15

Dose

Condylomata acuminata affecting the penis or the female external genitalia

Child 2–18 years (see notes above) apply twice daily for 3 consecutive days; treatment may be repeated at weekly intervals if necessary for a total of four 3-day treatment courses; direct medical supervision for lesions greater than 4 cm²; max. 50 single applications ('loops') per session (consult product literature)

13.8 Sunscreens and camouflagers

13.8.1 Sunscreen preparations

13.8.2 Camouflagers

13.8.1 Sunscreen preparations

Solar ultraviolet irradiation can be harmful to the skin. It is responsible for disorders such as *polymorphic light eruption*, *solar urticaria*, and it provokes the various *cutaneous porphyrias*. It also provokes (or at least aggravates) skin lesions of *lupus erythematosus* and may aggravate some other *dermatoses*. Certain drugs, such as demeclocycline, phenothiazines, or amiodarone, can cause photosensitivity. All these conditions (as well as *sunburn*) may occur after relatively short periods of exposure to the sun. Solar ultraviolet irradiation may provoke attacks of recurrent herpes labialis (but it is not known whether the effect of sunlight exposure is local or systemic).

The effects of exposure over longer periods include *ageing changes* and more importantly the initiation of *skin cancer*.

Solar ultraviolet radiation is approximately 200–400 nm in wavelength. The medium wavelengths (290–320 nm, known as UVB) cause *sunburn*. The long wavelengths (320–400 nm, known as UVA) are responsible for many *photosensitivity reactions* and *photodermatoses*. Both UVA and UVB contribute to long-term *photodamage* and to the changes responsible for *skin cancer* and ageing.

Sunscreen preparations contain substances that protect the skin against UVA and UVB radiation, but they are no substitute for covering the skin and avoiding sunlight. Protective clothing and sun avoidance (rather than the use of sunscreen preparations) are recommended for children under 6 months of age.

The sun protection factor (SPF, usually indicated in the preparation title) provides guidance on the degree of protection offered against UVB; it indicates the multiples of protection provided against burning, compared with unprotected skin; for example, an SPF of 8 should enable a child to remain 8 times longer in the sun without burning. However, in practice users do not apply sufficient sunscreen product and the protection is lower than that found in experimental studies. Some manufacturers use a star rating system to indicate the protection against UVA relative to protection against UVB for sunscreen products. However, the usefulness of the star rating system remains controversial. The EU Commission (September 2006) has recommended that the UVA protection factor for a sunscreen should be at least one-third of the sun protection factor (SPF); products that achieve this requirement will be labelled with a UVA logo alongside the SPF classification. Preparations that also contain reflective substances, such as titanium dioxide, provide the most effective protection against UVA.

Sunscreen preparations may rarely cause allergic reactions.

For optimum photoprotection, sunscreen preparations should be applied **thickly** and **frequently** (approximately 2 hourly). In photodermatoses, they should be used from spring to autumn. As maximum protection from sunlight is desirable, preparations with the highest SPF should be prescribed.

Ingredient nomenclature in sunscreen preparations

rINN	INCI
amiloxate	isoamyl <i>p</i> -methoxycinnamate
avobenzene	butyl methoxydibenzoylmethane
bemotrizinol	bis-ethylhexyloxyphenol methoxyphenyl triazine
bisocotrizole	methylene bis-benzotriazolyl tetramethylbutylphenol
ecamsule	terephthalylidene dicamphor sulfonic acid
ensulizole	phenylbenzimidazole sulfonic acid
enzacamene	4-methylbenzylidene camphor
octinoxate	octyl (or ethylhexyl) methoxycinnamate
octocrilene	octocrylene
oxybenzone	benzophenone-3

The European Commission Cosmetic Products Regulation (EC) 1223/2009 requires the use of INCI (International Nomenclature of Cosmetic Ingredients) for cosmetics and sunscreens. This table includes the rINN and the INCI synonym for the active ingredients of sunscreen preparations in BNFC

Borderline substances The preparations marked 'ACBS' cannot be prescribed on the NHS except for skin protection against ultraviolet radiation in abnormal cutaneous photosensitivity resulting from genetic disorders or photodermatoses, including vitiligo and those resulting from radiotherapy; chronic or recurrent herpes simplex labialis. Preparations with SPF less than 30 should not normally be prescribed. See also Appendix 2.

Anthelios® (L'Oréal Active)

XL SPF 50+ Melt-in cream (UVA and UVB protection; UVB-SPF 50+), avobenzene 3.5%, bemotrizinol 3%, drometrizole trisiloxane 0.5%, ecamsule 1%, octocrilene 2.5%, titanium dioxide 4.2%, net price 50 mL = £3.63. ACBS

Excipients include disodium edetate, stearyl alcohol

Note For INCI synonyms, see table above

Sunsense® Ultra (Crawford)

Lotion (UVA and UVB protection; UVB-SPF 50+), avobenzene 2%, ensulizole 2%, enzacamene 4%, octinoxate 6%, oxybenzone 2%, titanium dioxide 3%, net price 50-mL bottle with roll-on applicator = £5.01, 125 mL = £8.14, 500-mL pump pack = £18.17. ACBS

Excipients include butylated hydroxytoluene, cetyl alcohol, fragrance, hydroxybenzoates (parabens), propylene glycol

Note For INCI synonyms, see table above

Uvistat® (LPC)

Cream (UVA and UVB protection; UVB-SPF 30), avobenzone 5%, bisotrizole 1.5%, octinoxate 7.5%, octocilene 4%, titanium dioxide 5.2%, net price 125 mL = £7.45. ACBS

Excipients include disodium edetate, hydroxybenzoates (parabens), propylene glycol

Note For INCI synonyms, see table above

Cream (UVA and UVB protection; UVB-SPF 50), amiloxate 2%, avobenzone 5%, bisotrizole 6%, octinoxate 10%, octocilene 4%, titanium dioxide 4.8%, net price 125 mL = £8.45. ACBS

Excipients include disodium edetate, polysorbate 60, propylene glycol

Note For INCI synonyms, see table above

Lipscreen (UVA and UVB protection; UVB-SPF 50), avobenzone 5%, bemotrizinol 3%, octinoxate 10%, octocilene 4%, titanium dioxide 3%, net price 5 g = £2.99. ACBS

Excipients include butylated hydroxytoluene, hydroxybenzoates (parabens)

Note For INCI synonyms, see table above

Photodamage

Actinic keratoses occur very rarely in healthy children; *actinic cheilitis* may occur on the lips of adolescents following excessive sun exposure.

Diclofenac gel (*Solaraze*®) and topical preparations of **fluorouracil** are licensed for the treatment of actinic keratoses but they are not licensed for use in children.

In children with photosensitivity disorders, such as erythropoietic protoporphyria, specialists may use **betacarotene**, **mepacrine**, **chloroquine** or **hydroxychloroquine** (section 10.1.3) to reduce skin reactions.

BETACAROTENE

Note Betacarotene is a precursor to vitamin A

Cautions monitor vitamin A intake; **interactions:**

Appendix 1 (vitamins)

Hepatic impairment avoid

Renal impairment use with caution

Pregnancy partially converted to vitamin A, but does not give rise to abnormally high serum concentration; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding use with caution—present in milk

Side-effects loose stools; yellow discoloration of skin; rarely, bruising, arthralgia

Licensed use not licensed for use in UK

Indications and dose

Management of photosensitivity reactions in erythropoietic protoporphyria (specialist use only)

• By mouth

Child 1–5 years 60–90 mg daily in single or divided doses

Child 5–9 years 90–120 mg daily in single or divided doses

Child 9–12 years 120–150 mg daily in single or divided doses

Child 12–16 years 150–180 mg daily in single or divided doses

Child 16–18 years 180–300 mg daily in single or divided doses

Note Protection not total—avoid strong sunlight and use sunscreen preparations; generally 2–6 weeks of

treatment (resulting in yellow coloration of palms and soles) necessary before increasing exposure to sunlight; dose should be adjusted according to level of exposure to sunlight

Betacarotene (Non-proprietary)

Capsules, 15 mg, 25 mg are available from 'special-order' manufacturers or specialist importing companies, see p. 840. Label: 21

13.8.2 Camouflagers

Disfigurement of the skin can be very distressing and may have a marked psychological effect, especially in children. Cosmetic preparations may be used to camouflage unsightly scars, skin deformities, and pigment abnormalities, such as vitiligo and birthmarks.

Opaque cover foundation or cream is used to mask skin pigment abnormalities; careful application using a combination of dark- and light-coloured cover creams set with powder helps to minimise the appearance of skin deformities.

Borderline substances The preparations marked 'ACBS' cannot be prescribed on the NHS for postoperative scars and other deformities except as adjunctive therapy in the relief of emotional disturbances due to disfiguring skin disease, such as vitiligo.

Covermark® (Derma UK)

Classic foundation (masking cream), net price 15 mL (10 shades) = £11.86. ACBS

Excipients include beeswax, hydroxybenzoates (parabens), fragrance

Finishing powder, net price 25 g = £11.86. ACBS

Excipients include beeswax, hydroxybenzoates (parabens), fragrance

DermaBlend® (L'Oréal Active)

Ultra corrective foundation, (7 shades), net price 12 g = £5.60. ACBS

Excipients include beeswax, isopropyl palmitate

DermaColor® (Fox)

Camouflage creme, (100 shades), net price 25 mL = £10.52. ACBS

Excipients include beeswax, butylated hydroxytoluene, fragrance, propylene glycol, stearyl alcohol, wool fat

Fixing powder, (7 shades), net price 60 g = £9.05. ACBS

Excipients include fragrance

Keromask® (Lornamead)

Masking cream, (24 shades), net price 15 mL = £5.68. ACBS

Excipients include butylated hydroxyanisole, hydroxybenzoates (parabens), wool fat, propylene glycol

Finishing powder, (4 shades) net price 20 g = £5.68. ACBS

Excipients include butylated hydroxytoluene, hydroxybenzoates (parabens)

Veil® (Thomas Blake)

Cover cream (40 shades), net price 19 g = £22.42, 44 g = £33.35, 70 g = £42.10. ACBS

Excipients include hydroxybenzoates (parabens), wool fat derivative

Finishing powder, translucent, net price 35 g = £24.58. ACBS

Excipients include butylated hydroxyanisole, hydroxybenzoates (parabens)

13.9 Shampoos and other preparations for scalp conditions

The detergent action of shampoo removes grease (sebum) from hair. Prepubertal children produce very little grease and require shampoo less frequently than adults. Shampoos can be used as vehicles for medicinal products, but their usefulness is limited by the short time the product is in contact with the scalp and by their irritant nature.

Oils and ointments are very useful for scaly, dry scalp conditions; if a greasy appearance is cosmetically unacceptable, the preparation may be applied at night and washed out in the morning. Alcohol-based lotions are rarely used in children; alcohol causes painful stinging on broken skin and the fumes may exacerbate asthma.

Itchy, inflammatory, eczematous scalp conditions may be relieved by a simple emollient oil such as **olive oil** or **coconut oil** (arachis oil (ground nut oil, peanut oil) is best avoided in children under 5 years). In more severe cases a topical **corticosteroid** (section 13.4) may be required. Preparations containing **coal tar** are used for the common scaly scalp conditions of childhood including seborrhoeic dermatitis, dandruff (a mild form of seborrhoeic dermatitis), and psoriasis (section 13.5.2); **salicylic acid** is used as a keratolytic in some scalp preparations.

Shampoos containing antimicrobials such as **selenium sulfide** or **ketoconazole** are used for seborrhoeic dermatitis and dandruff in which yeast infection has been implicated, and for tinea capitis (ringworm of the scalp, section 13.10.2). Bacterial infection affecting the scalp (usually secondary to eczema, head lice, or ringworm) may be treated with shampoos containing antimicrobials such as **pyrithione zinc**, **cetrimide**, or **povidone-iodine**.

In neonates and infants, **cradle cap** (which is also a form of seborrhoeic eczema) can be treated by massaging **coconut oil** or **olive oil** into the scalp; a bland emollient such as **emulsifying ointment** can be rubbed onto the affected area once or twice daily before bathing and a mild shampoo used.

Shampoos

¹**Ketoconazole** (Non-proprietary) [PoM]

Shampoo, ketoconazole 2%, net price 120 mL = £3.27

Excipients include imidurea

Brands include Dandrazol® 2% Shampoo, Nizoral®

Dose

Seborrhoeic dermatitis and dandruff

Child 12–18 years treatment, apply twice weekly for 2–4 weeks; prophylaxis, apply once every 1–2 weeks; leave preparation on for 3–5 minutes before rinsing

Pityriasis versicolor

Child 12–18 years treatment, apply once daily for max. 5 days; prophylaxis, apply once daily for up to 3 days before sun exposure; leave preparation on for 3–5 minutes before rinsing

Alphosyl 2 in 1[®] (GSK Consumer Healthcare)

Shampoo, alcoholic coal tar extract 5%, net price 125 mL = £1.89, 250 mL = £4.52

Excipients include hydroxybenzoates (parabens), fragrance

Dose

Dandruff

Use once or twice weekly as necessary

Psoriasis, seborrhoeic dermatitis, scaling and itching

Use every 2–3 days

Capasal[®] (Dermal)

Shampoo, coal tar 1%, coconut oil 1%, salicylic acid 0.5%, net price 250 mL = £4.69

Excipients none as listed in section 13.1.3

Dose

Scaly scalp disorders including psoriasis, seborrhoeic dermatitis, dandruff, and cradle cap

Apply daily as necessary

Ceanel Concentrate[®] (Alliance)

Shampoo, cetrimide 10%, undecenoic acid 1%, net price 150 mL = £3.40, 500 mL = £9.80

Excipients none as listed in section 13.1.3

Dose

Scalp psoriasis, seborrhoeic dermatitis, dandruff

Apply 3 times in first week then twice weekly

Dermax[®] (Dermal)

Shampoo, benzalkonium chloride 0.5%, net price 250 mL = £5.69

Excipients none as listed in section 13.1.3

Dose

Seborrhoeic scalp conditions associated with dandruff and scaling

Apply as necessary

Psoriderm[®] (Dermal)

Scalp lotion (= shampoo), coal tar 2.5%, lecithin 0.3%, net price 250 mL = £4.74

Excipients include disodium edetate

Dose

Scalp psoriasis

Use as necessary

Selsun[®] (Chattam UK)

Shampoo, selenium sulfide 2.5%, net price 50 mL = £1.44, 100 mL = £1.96, 150 mL = £2.75

Excipients include fragrance

Cautions avoid using 48 hours before or after applying hair colouring, straightening or waving preparations

Dose

Seborrhoeic dermatitis and dandruff

Child 5–18 years apply twice weekly for 2 weeks then once weekly for 2 weeks and then as necessary

Pityriasis versicolor [unlicensed indication]

Child 5–18 years apply to affected area and leave on for 10 minutes before rinsing off; apply once daily for 7 days; repeat course if necessary

Note diluting with a small amount of water prior to application can reduce irritation

1. Can be sold to the public for the prevention and treatment of dandruff and seborrhoeic dermatitis of the scalp as a shampoo formulation containing ketoconazole max. 2%, in a pack containing max. 120 mL and labelled to show a max. frequency of application of once every 3 days

T/Gel® (J&J)

Shampoo, coal tar extract 2%, net price 125 mL = £3.61, 250 mL = £5.12

Excipients include fragrance, hydroxybenzoates (parabens), imidurea, tetrasodium edetate

Dose

Scalp psoriasis, seborrhoeic dermatitis, dandruff

Apply 2–3 times weekly

■ **Other scalp preparations****Cocals®**

Section 13.5.2

Polylar® (GSK)

Liquid, tar blend 1%, net price 250 mL = £2.23

Excipients include arachis (peanut) oil, fragrance, imidurea, polysorbate 80

Dose

Scalp disorders including psoriasis, seborrhoea, eczema, pruritus, and dandruff

Apply 1–2 times weekly

Polylar Plus® (GSK)

Liquid, tar blend 1%, net price 500 mL = £3.91

Excipients include arachis (peanut) oil, fragrance, imidurea, polysorbate 80

Dose

Scalp disorders including psoriasis, seborrhoea, pruritus, and dandruff

Apply 1–2 times weekly

Sebco®

Section 13.5.2

13.10 Anti-infective skin preparations

13.10.1 Antibacterial preparations

13.10.2 Antifungal preparations

13.10.3 Antiviral preparations

13.10.4 Parasitocidal preparations

13.10.5 Preparations for minor cuts and abrasions

13.10.1 Antibacterial preparations

13.10.1.1 Antibacterial preparations only used topically

13.10.1.2 Antibacterial preparations also used systemically

Topical antibacterial preparations are used to treat localised bacterial skin infections caused by Gram-positive organisms (particularly by staphylococci or streptococci). Systemic antibacterial treatment (Table 1, section 5.1) is more appropriate for deep-seated skin infections.

Problems associated with the use of topical antibacterials include bacterial resistance, contact sensitisation, and superinfection. In order to minimise the development of resistance, antibacterials used systemically (e.g. fusidic acid) should not generally be chosen for topical use. *Resistant organisms* are more common in hospitals, and whenever possible swabs should be taken for bacteriological examination before beginning treatment.

Neomycin applied topically may cause sensitisation and cross-sensitivity with other aminoglycoside antibac-

terials such as gentamicin may occur. Topical antibacterials applied over large areas can cause systemic toxicity; ototoxicity with neomycin and with **polymyxins** is a particular risk for neonates and children with renal impairment.

Superficial bacterial infection of the skin may be treated with a topical antiseptic such as **povidone-iodine** (section 13.11.4) which also softens crusts, or **hydrogen peroxide** 1% cream (section 13.11.6).

Bacterial infections such as *impetigo* and *folliculitis* can be treated with a short course of topical **fusidic acid**; **mupirocin** should be used only to treat meticillin-resistant *Staphylococcus aureus*.

For extensive or long-standing *impetigo*, an oral antibacterial such as **flucloxacillin** (or **clarithromycin** in children with penicillin-allergy), Table 1, section 5.1, should be used. A mild antiseptic may help to soften crusts. Mild antiseptics may be useful in reducing the spread of infection, but there is little evidence to support the use of topical antiseptics alone in the treatment of *impetigo*.

Cellulitis, a rapidly spreading deeply seated inflammation of the skin and subcutaneous tissue, requires systemic antibacterial treatment (see Table 1, section 5.1). Lower leg infections or infections spreading around wounds are almost always *cellulitis*. *Erysipelas*, a superficial infection with clearly defined edges (and often affecting the face), is also treated with a systemic antibacterial (see Table 1, section 5.1).

Staphylococcal scalded-skin syndrome requires urgent treatment with a systemic antibacterial, such as flucloxacillin (see Table 1, section 5.1).

Mupirocin is not related to any other antibacterial in use; it is effective for skin infections, particularly those due to Gram-positive organisms but it is not indicated for pseudomonal infection. Although *Staphylococcus aureus* strains with low-level resistance to mupirocin are emerging, it is generally useful in infections resistant to other antibacterials. To avoid the development of resistance, mupirocin or fusidic acid should not be used for longer than 10 days and local microbiology advice should be sought before using it in hospital. In the presence of mupirocin-resistant MRSA infection, a topical antiseptic, such as povidone-iodine, chlorhexidine, or alcohol, can be used (section 13.11); their use should be discussed with the local microbiologist.

Mupirocin ointment contains macrogols; extensive absorption of macrogols through the mucous membranes or through application to thin or damaged skin may result in renal toxicity, especially in neonates. Mupirocin nasal ointment is formulated in a paraffin base and may be more suitable for the treatment of MRSA-infected open wound in neonates.

Metronidazole gel is used topically in children to reduce the odour associated with anaerobic infections and for the treatment of periorificial rosacea (section 13.6); oral metronidazole (section 5.1.11) is used to treat wounds infected with anaerobic bacteria.

Retapamulin can be used for *impetigo* and other superficial bacterial skin infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes* that are resistant to first-line topical antibacterials. However, it is not effective against MRSA. The *Scottish Medicines Consortium* (p. 3) has advised (March 2008) that retapamulin (*Altargo*®) is not recommended for use within NHS Scotland for the treatment of superficial skin infections.

Silver sulfadiazine is licensed for the prevention and treatment of infection in burns but the use of appropriate dressings may be more effective. Systemic effects may occur following extensive application of silver sulfadiazine; its use is not recommended in neonates.

13.10.1.1 Antibacterial preparations only used topically

MUPIROCIN

Renal impairment manufacturer advises caution when mupirocin ointment used in moderate or severe impairment because it contains macrogols (polyethylene glycols)

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk—no information available

Breast-feeding no information available

Side-effects local reactions including urticaria, pruritus, burning sensation, rash

Licensed use mupirocin ointment licensed for use in children (age range not specified by manufacturer); *Bactroban*[®] cream not recommended for use in children under 1 year

Indications and dose

Bacterial skin infections (see also notes above)

Child 1 month–18 years apply up to 3 times daily for up to 10 days

Mupirocin (Non-proprietary) (PoM)

Ointment, mupirocin 2%, net price 15 g = £5.32

Bactroban[®] (GSK) (PoM)

Cream, mupirocin (as mupirocin calcium) 2%, net price 15 g = £4.38

Excipients include benzyl alcohol, cetyl alcohol, stearyl alcohol

Ointment, mupirocin 2%, net price 15 g = £4.38

Excipients none as listed in section 13.1.3

Nasal ointment—section 12.2.3

NEOMYCIN SULFATE

Cautions large areas—if large areas of skin are being treated ototoxicity may be a hazard in children, particularly in those with renal impairment

Contra-indications neonates

Renal impairment see Cautions above

Side-effects sensitisation (see also notes above)

Licensed use *Neomycin Cream BPC*—no information available

Indications and dose

Bacterial skin infections see under preparation

Neomycin Cream BPC (PoM) 

Cream, neomycin sulfate 0.5%, cetomacrogol emulsifying ointment 30%, chlorocresol 0.1%, disodium edetate 0.01%, in freshly boiled and cooled purified water, net price 15 g = £2.17

Excipients include cetostearyl alcohol, edetic acid (EDTA)

Dose

Apply up to 3 times daily (short-term use)

POLYMYXINS

Cautions large areas—if large areas of skin are being treated nephrotoxicity and neurotoxicity may be a hazard, particularly in children with renal impairment

Renal impairment see Cautions above

Side-effects sensitisation (see also notes above)

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Bacterial skin infections see under preparation

Polyfax[®] (TEVA UK) (PoM)

Ointment, polymyxin B sulfate 10 000 units, bacitracin zinc 500 units/g, net price 4 g = £3.26, 20 g = £4.62

Excipients none as listed in section 13.1.3

Dose

Apply twice daily or more frequently if required

RETAPAMULIN

Contra-indications contact with eyes and mucous membranes

Side-effects local reactions including irritation, erythema, pain, contact dermatitis, and pruritus

Indications and dose

Superficial bacterial skin infections (but see also notes above)

Child 9 months–18 years apply thinly twice daily for 5 days; max. area of skin treated 2% of body surface area; review treatment if no response within 2–3 days

Altargo[®] (GSK) (PoM)

Ointment, retapamulin 1%, net price 5 g = £7.89.

Label: 28

Excipients include butylated hydroxytoluene

SILVER SULFADIAZINE

Cautions G6PD deficiency; may inactivate enzymatic debriding agents—concomitant use may be inappropriate; **interactions:** Appendix 1 (sulfonamides)

Large areas Plasma-sulfadiazine concentrations may approach therapeutic levels with *side-effects* and *interactions* as for sulfonamides (see section 5.1.8) if large areas of skin are treated. Owing to the association of sulfonamides with severe blood and skin disorders, treatment should be stopped immediately if blood disorders or rashes develop—but leucopenia developing 2–3 days after starting treatment of burns patients is reported usually to be self-limiting and silver sulfadiazine need not usually be discontinued provided blood counts are monitored carefully to ensure return to baseline within a few days. Argryria may also occur if large areas of skin are treated (or if application is prolonged).

Contra-indications sensitivity to sulfonamides; not recommended for neonates

Hepatic impairment manufacturer advises caution if significant impairment; see also Large areas, above

Renal impairment manufacturer advises caution if significant impairment; see also Large areas, above

Pregnancy risk of neonatal haemolysis and methaemoglobinaemia in third trimester

Breast-feeding small risk of kernicterus in jaundiced infants and of haemolysis in G6PD deficient infants

Side-effects allergic reactions including burning, itching and rashes; argyria reported following prolonged use; leucopenia reported (monitor blood count)

Licensed use no age range specified by manufacturer but see contra-indications, above

Indications and dose

Prophylaxis and treatment of infection in burn wounds, for conservative management of finger-tip injuries see under preparation below

Adjunct to short-term treatment of infection in pressure sores, adjunct to prophylaxis of infection in skin graft donor sites and extensive abrasions consult product literature for details

Flamazine® (S&N Hlth.) (PoM)

Cream, silver sulfadiazine 1%, net price 20 g = £2.91, 50 g = £3.85, 250 g = £10.32, 500 g = £18.27

Excipients include cetyl alcohol, polysorbates, propylene glycol
Dose

Burns

Child 1 month–18 years apply daily or more frequently if very exudative

Finger-tip injuries

Child 1 month–18 years apply every 2–3 days

Note apply with sterile applicator

13.10.1.2 Antibacterial preparations also used systemically

Sodium fusidate is a narrow-spectrum antibacterial used for staphylococcal infections. For the role of sodium fusidate in the treatment of impetigo see p. 591.

Metronidazole is used topically to treat rosacea and to reduce the odour associated with anaerobic infections; oral metronidazole (section 5.1.11) is used to treat wounds infected with anaerobic bacteria.

Angular cheilitis An ointment containing sodium fusidate is used in the fissures of angular cheilitis when associated with staphylococcal infection. For further information on angular cheilitis, see p. 552.

FUSIDIC ACID

Cautions see notes above; avoid contact with eyes

Side-effects rarely hypersensitivity reactions

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Staphylococcal skin infections

Apply 3–4 times daily, usually for 7 days

Penicillin-resistant staphylococcal infections

section 5.1.7

Staphylococcal eye infections

section 11.3.1

Fucidin® (LEO) (PoM)

Cream, fusidic acid 2%, net price 15 g = £1.92, 30 g = £3.59

Excipients include butylated hydroxyanisole, cetyl alcohol

Ointment, sodium fusidate 2%, net price 15 g = £2.23, 30 g = £3.79

Excipients include cetyl alcohol, wool fat

Dental prescribing on NHS May be prescribed as Sodium Fusidate ointment

METRONIDAZOLE

Cautions avoid exposure to strong sunlight or UV light

Side-effects skin irritation

Licensed use *Acea*® and *Anabact*® not licensed for use in children under 12 years; *Noritate*® not licensed for use in children under 16 years; *Metrogel*®, *Metro-sa*®, *Rosiced*®, *Rozex*®, and *Zyomet*® not licensed for use in children

Indications and dose

Malodorous tumours and wounds

For dose see preparations

Rosacea (see also section 13.6)

For dose see preparations

Helicobacter pylori eradication

section 1.3

Anaerobic infections

section 5.1.11 and section 7.2.2

Protozoal infections

section 5.4.2

Acea® (Fendale) (PoM)

Gel, metronidazole 0.75%, net price 40 g = £9.95

Excipients include disodium edetate, hydroxybenzoates (parabens)

Dose

Acute inflammatory exacerbations of rosacea

Child 1–18 years apply thinly twice daily

Anabact® (CHS) (PoM)

Gel, metronidazole 0.75%, net price 15 g = £4.47, 30 g = £7.89

Excipients include hydroxybenzoates (parabens), propylene glycol

Dose

Malodorous fungating tumours and skin ulcers

Apply to clean wound 1–2 times daily and cover with non-adherent dressing

Metrogel® (Galderma) (PoM)

Gel, metronidazole 0.75%, net price 40 g = £22.63

Excipients include hydroxybenzoates (parabens), propylene glycol

Dose

Acute inflammatory exacerbations of rosacea

Child 1–18 years apply thinly twice daily

Malodorous fungating tumours

Apply to clean wound 1–2 times daily and cover with non-adherent dressing

Metrosa® (Lindera) (PoM)

Gel, metronidazole 0.75%, net price 40 g = £19.90

Excipients include propylene glycol

Dose

Acute exacerbation of rosacea

Child 1–18 years apply thinly twice daily

Rosiced® (Fabre) (PoM)

Cream, metronidazole 0.75%, net price 30 g = £7.50

Excipients include propylene glycol

Dose

Inflammatory papules and pustules of rosacea

Child 1–18 years apply twice daily for 6 weeks (longer if necessary)

Rozex® (Galderma) **[PoM]**

Cream, metronidazole 0.75%, net price 30 g = £6.60, 40 g = £9.88

Excipients include benzyl alcohol, isopropyl palmitate

Gel, metronidazole 0.75%, net price 30 g = £6.60, 40 g = £9.88

Excipients include disodium edetate, hydroxybenzoates (parabens), propylene glycol

Dose

Inflammatory papules, pustules and erythema of rosacea

Child 1–18 years apply twice daily

Zyomet® (AMCo) **[PoM]**

Gel, metronidazole 0.75%, net price 30 g = £12.00

Excipients include benzyl alcohol, disodium edetate, propylene glycol

Dose

Acute inflammatory exacerbations of rosacea

Child 1–18 years apply thinly twice daily

13.10.2 Antifungal preparations

Most localised fungal infections are treated with topical preparations. To prevent relapse, local antifungal treatment should be continued for 1–2 weeks after the disappearance of all signs of infection. Systemic therapy (section 5.2) is necessary for scalp infection or if the skin infection is widespread, disseminated or intractable; although topical therapy may be used to treat some nail infections, systemic therapy (section 5.2) is more effective. Specimens of scale, nail or hair should be sent for mycological examination before starting treatment, unless the diagnosis is certain.

Dermatophytoses Ringworm infection can affect the scalp (tinea capitis), body (tinea corporis), groin (tinea cruris), hand (tinea manuum), foot (tinea pedis, athlete's foot), or nail (tinea unguium, onychomycosis). Tinea capitis is a common childhood infection that requires systemic treatment with an oral antifungal (section 5.2); additional application of a topical antifungal, during the early stages of treatment, may reduce the risk of transmission. A topical antifungal can also be used to treat asymptomatic carriers of scalp ringworm.

Tinea corporis and tinea pedis infections in children respond to treatment with a topical **imidazole** (clotrimazole, econazole, or miconazole) or **terbinafine** cream. Nystatin is less effective against tinea.

Compound benzoic acid ointment (Whitfield's ointment) has been used for ringworm infections but it is cosmetically less acceptable than proprietary preparations. Antifungal dusting powders are of little therapeutic value in the treatment of fungal skin infections and may cause skin irritation; they may have some role in preventing re-infection.

Antifungal treatment may not be necessary in asymptomatic children with tinea infection of the nails. If treatment is necessary, a systemic antifungal (section 5.2) is more effective than topical therapy. However, topical application of **tioconazole** may be useful for treating early onychomycosis when involvement is limited to mild distal disease, or for superficial white onychomycosis, or where there are contra-indications to systemic therapy. Chronic paronychia on the fingers (usually due to a candidal infection) should be treated with topical clotrimazole or nystatin, but these preparations should be used with caution in children who suck their

fingers. Chronic paronychia of the toes (usually due to dermatophyte infection) can be treated with topical terbinafine.

Pityriasis versicolor Pityriasis (tinea) versicolor can be treated with **ketoconazole** shampoo or **selenium sulfide** shampoo (section 13.9). Topical imidazole antifungals such as **clotrimazole**, **econazole**, and **miconazole**, or topical **terbinafine** are alternatives, but large quantities may be required.

If topical therapy fails, or if the infection is widespread, pityriasis versicolor is treated systemically with an azole antifungal (section 5.2). Relapse is common, especially in the immunocompromised.

Candidiasis Candidal skin infections can be treated with topical imidazole antifungals **clotrimazole**, **econazole**, or **miconazole**; topical terbinafine is an alternative. Topical application of **nystatin** is also effective for candidiasis but it is ineffective against dermatophytosis. Refractory candidiasis requires systemic treatment (section 5.2.1) generally with a triazole such as fluconazole; systemic treatment with griseofulvin or terbinafine is **not appropriate** for refractory candidiasis. For the treatment of oral candidiasis see section 12.3.2 and for the management of nappy rash see section 13.2.2.

Angular cheilitis Miconazole cream is used in the fissures of angular cheilitis when associated with *Candida*. For further information on angular cheilitis, see p. 552.

Cautions Contact with eyes and mucous membranes should be avoided.

Side-effects Occasional local irritation and hypersensitivity reactions include mild burning sensation, erythema, and itching. Treatment should be discontinued if symptoms are severe.

Compound topical preparations Combination of an imidazole and a mild corticosteroid (such as hydrocortisone 1%) (section 13.4) may be of value in the treatment of eczematous intertrigo and, in the first few days only, of a severely inflamed patch of ringworm. Combination of a mild corticosteroid with either an imidazole or nystatin may be of use in the treatment of *intertriginous eczema* associated with candida.

AMOROLFINE

Cautions see notes above; also avoid contact with ears; use with caution in child likely to suck affected digits

Side-effects see notes above

Licensed use not licensed for use in children under 12 years

Indications and dose**Fungal nail infections**

Apply to infected nails 1–2 times weekly after filing and cleansing; allow to dry (approx. 3 minutes); treat finger nails for 6 months, toe nails for 9–12 months (review at intervals of 3 months); avoid nail varnish or artificial nails during treatment

Amorolfine (Non-proprietary) **[PoM]**

Nail lacquer, amorolfine (as hydrochloride) 5%, net price 5-mL pack = £14.86, 2 × 2.5-mL pack = £19.53. Label: 10, patient information leaflet

Brands include Omicur®

Loceryl® (Galderma) (POM)

Nail lacquer, amorolfine (as hydrochloride) 5%, net price 5-mL pack (with nail files, spatulas, and cleansing swabs) = £9.08. Label: 10, patient information leaflet

Excipients none as listed in section 13.1.3

BENZOIC ACID

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Ringworm (tinea) but see notes above; dose under preparation

With salicylic acid

For prescribing information on salicylic acid, see p. 577

Benzoic Acid Ointment, Compound, BP (Whitfield's ointment)

Ointment, benzoic acid 6%, salicylic acid 3%, in emulsifying ointment

Excipients include cetostearyl alcohol

Dose

Child 1 month–18 years apply twice daily

CLOTRIMAZOLE

Cautions see notes above

Pregnancy minimal absorption from skin; not known to be harmful

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Fungal skin infections

Apply 2–3 times daily

Vaginal candidiasis section 7.2.2

Otitis externa section 12.1.1

Clotrimazole (Non-proprietary)

Cream, clotrimazole 1%, net price 20 g = £1.26

Canesten® (Bayer Consumer Care)

Cream, clotrimazole 1%, net price 20 g = £2.14, 50 g = £3.50

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbate 60

Solution, clotrimazole 1% in macrogol 400 (polyethylene glycol 400), net price 20 mL = £2.30. For hairy areas

Excipients none as listed in section 13.1.3

Spray, clotrimazole 1%, in 30% isopropyl alcohol, net price 40-mL atomiser = £4.72. Label: 15. For large or hairy areas

Excipients include propylene glycol

ECONAZOLE NITRATE

Cautions see notes above

Pregnancy minimal absorption from skin; not known to be harmful

Side-effects see notes above

Licensed use **Pevaryl®**, no age range specified by manufacturer

Indications and dose

Fungal skin infections

Apply twice daily

Fungal nail infections

Apply once daily under occlusive dressing

Vaginal candidiasis section 7.2.2

Pevaryl® (Janssen)

Cream, econazole nitrate 1%, net price 30 g = £3.71

Excipients include butylated hydroxyanisole, fragrance

MICONAZOLE NITRATE

Cautions see notes above; **interactions:** Appendix 1 (antifungals, imidazole)

Pregnancy absorbed from skin in small amounts; manufacturer advises caution

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Fungal skin infections

Neonate apply twice daily continuing for 10 days after lesions have healed

Child 1 month–18 years apply twice daily continuing for 10 days after lesions have healed

Fungal nail infections

Apply 1–2 times daily

Oral and intestinal fungal infections section 12.3.2

Vaginal candidiasis section 7.2.2

Miconazole (Non-proprietary)

Cream, miconazole nitrate 2%, net price 20 g =

£2.05, 45 g = £1.97

Dental prescribing on NHS Miconazole cream may be prescribed

Daktarin® (Janssen)

Cream, miconazole nitrate 2%, net price 30 g = £1.82

Excipients include butylated hydroxyanisole

NYSTATIN

Cautions see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Skin infections due to *Candida* spp. for dose, see preparation

Oral fungal infections section 12.3.2

Nystaform® (Typharm) (POM)

Cream, nystatin 100 000 units/g, chlorhexidine hydrochloride 1%, net price 30 g = £2.62

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbate 60

Dose

Apply 2–3 times daily continuing for 7 days after lesions have healed.

SALICYLIC ACID

Cautions avoid broken or inflamed skin

Salicylate toxicity Salicylate toxicity can occur particularly if applied on large areas of skin

Side-effects see notes above

Indications and dose

Fungal nail infections, particularly tinea

Child 5–18 years apply twice daily and after washing

Note Use with caution in child likely to suck affected digits

Hyperkeratotic skin disorders section 13.5.2

Warts and calluses section 13.7

Phytex[®] (Wynlit) 

Paint, salicylic acid 1.46% (total combined), tannic acid 4.89% and boric acid 3.12% (as borotannic complex), in a vehicle containing alcohol and ethyl acetate, net price 25 mL (with brush) = £2.97

Excipients none as listed in section 13.1.3

Note Flammable

TERBINAFINE

Cautions avoid contact with eyes

Pregnancy manufacturer advises use only if potential benefit outweighs risk—*animal* studies suggest no adverse effects

Breast-feeding manufacturer advises avoid—present in milk, but less than 5% of the dose is absorbed after topical application of terbinafine; avoid application to mother's chest

Side-effects see notes above

Licensed use not licensed for use in children

Indications and dose

Fungal skin infections

Apply thinly 1–2 times daily for up to 1 week in tinea pedis, 1–2 weeks in tinea corporis and tinea cruris, 2 weeks in cutaneous candidiasis and pityriasis versicolor; review after 2 weeks

Systemic therapy section 5.2.5

¹Terbinafine (Non-proprietary) 

Cream, terbinafine hydrochloride 1%, net price 15 g = £1.73, 30 g = £3.46

Lamisil[®] (Novartis Consumer Health) 

Cream, terbinafine hydrochloride 1%, net price 15 g = £4.86, 30 g = £8.76

Excipients include benzyl alcohol, cetyl alcohol, polysorbate 60, stearyl alcohol

TIOCONAZOLE

Cautions see notes above; also use with caution if child likely to suck affected digits

Pregnancy manufacturer advises avoid

- Can be sold to the public for external use in children over 16 years for the treatment of tinea pedis and tinea cruris as a cream containing terbinafine hydrochloride max. 1% in a pack containing max. 15 g; also for the treatment of tinea pedis, tinea cruris, and tinea corporis as a spray containing terbinafine hydrochloride max. 1% in a pack containing max. 30 mL or as a gel containing terbinafine hydrochloride max. 1% in a pack containing max. 30 g


Side-effects see notes above; also local oedema, dry skin, nail discoloration, periungual inflammation, nail pain, rash, exfoliation

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Fungal nail infections

Apply to nails and surrounding skin twice daily for up to 6 months (may be extended to 12 months)

Trosyl[®] (Pfizer) 

Cutaneous solution, tioconazole 28%, net price 12 mL (with applicator brush) = £27.38

Excipients none as listed in section 13.1.3

UNDECENOATES

Cautions see notes above; avoid broken skin

Side-effects see notes above

Licensed use *Monphytol[®]* not licensed for use in children under 12 years; *Mycota[®]* licensed for use in children (age range not specified by manufacturer)

Indications and dose

See under preparations

Mycota[®] (Thornton & Ross)

Cream, zinc undecenoate 20%, undecenoic acid 5%, net price 25 g = £1.64

Excipients include cetostearyl alcohol, fragrance

Dose

Treatment of athlete's foot

Apply twice daily continuing for 7 days after lesions have healed

Prevention of athlete's foot

Apply once daily

Powder, zinc undecenoate 20%, undecenoic acid 2%, net price 70 g = £2.22

Excipients include fragrance

Dose

Treatment of athlete's foot

Apply twice daily continuing for 7 days after lesions have healed

Prevention of athlete's foot

Apply once daily

Spray application, undecenoic acid 3.9%, dichlorophen 0.4% (pressurised aerosol pack), net price 100 mL = £2.46

Excipients include fragrance

Note Flammable

Dose

Treatment of athlete's foot

Apply twice daily continuing for 7 days after lesions have healed

Prevention of athlete's foot

Apply once daily

13.10.3 Antiviral preparations

See section 12.3.2 for drugs used in *herpetic stomatitis*, section 13.5.1 for *eczema herpeticum*, and section 11.3.3 for viral infections of the eye.

Aciclovir cream is used for the treatment of initial and recurrent labial, cutaneous, and genital *herpes simplex infections* in children; treatment should begin as early as

possible. Systemic treatment is necessary for buccal or vaginal infections or if cold sores recur frequently (for details of systemic use see section 5.3.2.1).

Herpes labialis **Aciclovir** cream can be used for the treatment of initial and recurrent labial herpes simplex infections (cold sores). It is best applied at the earliest possible stage, usually when prodromal changes of sensation are felt in the lip and before vesicles appear.

Penciclovir cream is also licensed for the treatment of herpes labialis; it needs to be applied more frequently than aciclovir cream.

ACICLOVIR

(Acyclovir)

Cautions avoid contact with eyes and mucous membranes

Pregnancy not known to be harmful—manufacturers advise use only when potential benefit outweighs risk; limited absorption from topical aciclovir preparations

Side-effects transient stinging or burning; occasionally erythema, itching or drying of the skin

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Herpes simplex infections

Apply to lesions every 4 hours (5 times daily) for 5–10 days, starting at first sign of attack

Herpes simplex and varicella–zoster infections section 5.3.2.1

Eye infections section 11.3.3

Aciclovir (Non-proprietary) (PoM)

Cream, aciclovir 5%, net price 2 g = 83p, 10 g = £4.15

Dental prescribing on NHS Aciclovir Cream may be prescribed

Note A 2-g tube and a pump pack are on sale to the public for the treatment of cold sores

Zovirax® (GSK) (PoM)

Cream, aciclovir 5%, net price 2 g = £4.63, 10 g = £13.96

Excipients include cetostearyl alcohol, propylene glycol

PENCICLOVIR

Cautions avoid contact with eyes and mucous membranes

Side-effects transient stinging, burning, numbness; hypersensitivity reactions also reported

Licensed use not licensed for use in children under 12 years

Vectavir® (Novartis Consumer Health) (PoM)

Cream, penciclovir 1%, net price 2 g = £4.20

Excipients include cetostearyl alcohol, propylene glycol
Dose

Herpes labialis

Apply to lesions every 2 hours during waking hours for 4 days, starting at first sign of attack

Dental prescribing on NHS May be prescribed as Penciclovir Cream

13.10.4 Parasitidal preparations

Suitable quantities of parasitidal preparations

Area of body	Skin creams	Lotions	Cream rinses
Scalp (head lice)	—	50–100 mL	50–100 mL
Body (scabies)	30–60 g	100 mL	—
Body (crab lice)	30–60 g	100 mL	—

These amounts are usually suitable for a child 12–18 years for single application

Scabies

Permethrin is used for the treatment of *scabies* (*Sarcoptes scabiei*); **malathion** can be used if permethrin is inappropriate.

Benzyl benzoate is an irritant and should be avoided in children; it is less effective than malathion and permethrin.

Ivermectin (available from 'special-order' manufacturers or specialist importing companies, see p. 840), is used in combination with topical drugs, for the treatment of hyperkeratotic (crusted or 'Norwegian') scabies that does not respond to topical treatment alone.

Application Although acaricides have traditionally been applied after a hot bath, this is **not** necessary and there is even evidence that a hot bath may increase absorption into the blood, removing them from their site of action on the skin.

All members of the affected household should be treated simultaneously. Treatment should be applied to the whole body including the scalp, neck, face, and ears. Particular attention should be paid to the webs of the fingers and toes and lotion brushed under the ends of nails. Malathion and permethrin should be applied twice, one week apart. It is important to warn users to reapply treatment to the hands if they are washed. Children with hyperkeratotic scabies may require 2 or 3 applications of acaricide on consecutive days to ensure that enough penetrates the skin crusts to kill all the mites.

Itching The *itch* and *eczema* of scabies persists for some weeks after the infestation has been eliminated and treatment for pruritus and eczema (section 13.5.1) may be required. Application of **crotamiton** can be used to control itching after treatment with more effective acaricides. A topical **corticosteroid** (section 13.4) may help to reduce itch and inflammation after scabies has been treated successfully; however, persistent symptoms suggest failure of scabies eradication. Oral administration of a **sedating antihistamine** (section 3.4.1) at night may also be useful.

Head lice

Dimeticone is effective against head lice (*Pediculus humanus capitis*) and acts on the surface of the organism. **Malathion**, an organophosphorous insecticide, is an alternative but resistance has been reported. Benzyl benzoate is licensed for the treatment of head lice but it is not recommended for use in children.

Head lice infestation (pediculosis) should be treated using lotion or liquid formulations only if live lice are present. Shampoos are diluted too much in use to be effective. A contact time of 8–12 hours or overnight treatment is recommended for lotions and liquids; a 2-hour treatment is not sufficient to kill eggs.

In general, a course of treatment for head lice should be 2 applications of a parasitocidal product 7 days apart to kill lice emerging from any eggs that survive the first application. All affected individuals in a household should be treated at the same time.

Wet combing methods Head lice can be mechanically removed by combing wet hair meticulously with a plastic detection comb (probably for at least 30 minutes each time) over the whole scalp at 4-day intervals for a minimum of 2 weeks and continued until no lice are found on 3 consecutive sessions; hair conditioner or vegetable oil can be used to facilitate the process.

Several devices for the removal of head lice, such as combs and topical solutions, are available and some are prescribable on the NHS (consult Drug Tariff—see Appliances and Reagents, p. 829 for links to online Drug Tariffs).

Crab lice

Permethrin and malathion are used to eliminate crab lice (*Phthirus pubis*); permethrin is not licensed for treatment of crab lice in children under 18 years. An aqueous preparation should be applied, allowed to dry naturally and washed off after 12 hours; a second treatment is needed after 7 days to kill lice emerging from surviving eggs. All surfaces of the body should be treated, including the scalp, neck, and face (paying particular attention to the eyebrows and other facial hair). A different insecticide should be used if a course of treatment fails.

Parasitocidal preparations

Dimeticone coats head lice and interferes with water balance in lice by preventing excretion of water; it is less active against eggs and treatment should be repeated after 7 days.

Malathion is recommended for scabies, head lice and crab lice (see notes above). The risk of systemic effects associated with 1–2 applications of malathion is considered to be very low; however, except in the treatment of hyperkeratotic scabies (see notes above), applications of malathion liquid repeated at intervals of less than 1 week or application for more than 3 consecutive weeks should be avoided since the likelihood of eradication of lice is not increased.

Permethrin is effective for scabies. It is active against head lice but the formulation and licensed methods of application of the current products make them unsuitable for the treatment of head lice. Permethrin is also effective against crab lice but it is not licensed for this purpose in children under 18 years.

DIMETICONE

Cautions avoid contact with eyes

Side-effects skin irritation

Licensed use not licensed for use in children under 6 months except under medical supervision

Indications and dose

Head lice

Rub into dry hair and scalp, allow to dry naturally, shampoo after 8 hours (or overnight); repeat application after 7 days

Hedrin[®] (Thornton & Ross)

Lotion, dimeticone 4%, net price 50 mL = £2.98, 120-mL spray pack = £7.13, 150 mL = £6.92

Note Patients should be told to keep their hair away from fire and flames during treatment

MALATHION

Cautions avoid contact with eyes; do not use on broken or secondarily infected skin; do not use lotion more than once a week for 3 consecutive weeks; alcoholic lotions **not** recommended for head lice in children with severe eczema or asthma, or for scabies or crab lice (see notes above)

Side-effects skin irritation and hypersensitivity reactions; chemical burns also reported

Licensed use not licensed for use in children under 6 months except under medical supervision

Indications and dose

See notes above and under preparations

Head lice

Rub into dry hair and scalp, allow to dry naturally, remove by washing after 12 hours; repeat application after 7 days (see also notes above)

Crab lice

Apply over whole body, allow to dry naturally, wash off after 12 hours or overnight; repeat application after 7 days

Scabies

Apply over whole body, and wash off after 24 hours; if hands are washed with soap within 24 hours, they should be retreated; see also notes above; repeat application after 7 days

Note For scabies, manufacturer recommends application to the body but not necessarily to the head and neck. However, application should be extended to the scalp, neck, face, and ears

Derbac-M[®] (SSL)

Liquid, malathion 0.5% in an aqueous basis, net price 50 mL = £3.05, 200 mL = £7.33

Excipients include cetostearyl alcohol, fragrance, hydroxybenzoates (parabens)

For crab lice, head lice, and scabies

PERMETHRIN

Cautions avoid contact with eyes; do not use on broken or secondarily infected skin

Side-effects pruritus, erythema, and stinging; rarely rashes and oedema

Licensed use **Dermal Cream** (scabies), not licensed for use in children under 2 months; children aged 2 months–2 years, medical supervision required; not licensed for treatment of crab lice in children under 18 years; **Crete Rinse** (head lice) not licensed for use in children under 6 months except under medical supervision

Indications and dose

See notes above

Scabies

Apply 5% preparation over whole body including face, neck, scalp and ears; wash off after 8–12 hours; if hands washed with soap within 8 hours of application, they should be treated again with cream (see notes above); repeat application after 7 days

Note Manufacturer recommends application to the body but to exclude head and neck. However, application should be extended to the scalp, neck, face, and ears

Permethrin (Non-proprietary)

Cream, permethrin 5%, net price 30 g = £6.96

Lyclear® Creme Rinse (Omega Pharma) 

Cream rinse, permethrin 1% in basis containing isopropyl alcohol 20%, net price 59 mL = £3.55, 2 × 59-mL pack = £6.46

Excipients include cetyl alcohol

Note Use not recommended, therefore no dose stated (product too diluted in use and insufficient contact time)

Lyclear® Dermal Cream (Omega Pharma)

Dermal cream, permethrin 5%, net price 30 g = £5.71. Label: 10, patient information leaflet

Excipients include butylated hydroxytoluene, wool fat derivative

13.10.5 Preparations for minor cuts and abrasions

Cetrimide cream is used to treat minor cuts and abrasions. **Proflavine** cream may be used to treat infected wounds or burns, but has now been largely superseded by other antiseptics or suitable antibacterials.

Cetrimide Cream, BP

Cream, cetrimide 0.5% in a suitable water-miscible basis such as cetostearyl alcohol 5%, liquid paraffin 50% in freshly boiled and cooled purified water, net price 50 g = £1.11

Proflavine Cream, BPC

Cream, proflavine hemisulfate 0.1%, yellow beeswax 2.5%, chlorocresol 0.1%, liquid paraffin 67.3%, freshly boiled and cooled purified water 25%, wool fat 5%, net price 100 mL = £2.40

Excipients include beeswax, wool fat

Note Stains clothing

Collodion

Flexible collodion may be used to seal minor cuts and wounds that have partially healed.

Collodion, Flexible, BP

Collodion, castor oil 2.5%, colophony 2.5% in a collodion basis, prepared by dissolving pyroxylin (10%) in a mixture of 3 volumes of ether and 1 volume of alcohol (90%), net price 10 mL = 38p. Label: 15

Contra-indications allergy to colophony in elastic adhesive plasters and tape

Skin tissue adhesive

Tissue adhesives are used for closure of minor skin wounds and for additional suture support. They should be applied by an appropriately trained healthcare professional. Skin tissue adhesives may cause skin sensitisation.

Dermabond ProPen® (Ethicon)

Topical skin adhesive, sterile, octyl 2-cyanoacrylate, net price 0.5 mL = £18.92

Epiglu® (Schuco)

Tissue adhesive, sterile, ethyl-2-cyanoacrylate 954.5 mg/g, polymethylmethacrylate, net price 4 × 3-g vials = £149.50 (with dispensing pipettes and palette)

Histoacryl® (B. Braun)

Tissue adhesive, sterile, enbucrilate, net price 5 × 200-mg unit (blue) = £32.00, 10 × 200-mg unit (blue) = £67.20, 5 × 500-mg unit (clear or blue) = £34.65, 10 × 500-mg unit (blue) = £69.30

LiquiBand® (MedLogic)

Tissue adhesive, sterile, enbucrilate, net price 0.5-g amp = £5.50

13.11 Skin cleansers, antiseptics, and desloughing agents

13.11.1 Alcohols and saline**13.11.2 Chlorhexidine salts****13.11.3 Cationic surfactants and soaps****13.11.4 Iodine****13.11.5 Phenolics****13.11.6 Oxidisers and dyes****13.11.7 Desloughing agents**

Soap or detergent is used with water to cleanse intact skin but they can irritate infantile skin; emollient preparations such as aqueous cream (section 13.2.1.1) or emulsifying ointment (section 13.2.1) can be used in place of soap or detergent for cleansing dry or irritated skin.

An antiseptic is used for skin that is infected or that is susceptible to recurrent infection. Detergent preparations containing **chlorhexidine** or **povidone-iodine**, which should be thoroughly rinsed off, are used. Emollients may also contain antiseptics (section 13.2.1).

Antiseptics such as **chlorhexidine** or **povidone-iodine** are used on intact skin before surgical procedures; their antiseptic effect is enhanced by an alcoholic solvent. Antiseptic solutions containing **cetrimide** can be used if a detergent effect is also required.

Preparations containing alcohol, and regular use of povidone-iodine, should be avoided on neonatal skin (see section 13.1).

Hydrogen peroxide, an oxidising agent, is available as a cream and can be used for superficial bacterial skin infections.

For irrigating ulcers or wounds, lukewarm sterile **sodium chloride 0.9% solution** is used but tap water is often appropriate.

Potassium permanganate solution 1 in 10 000, a mild antiseptic with astringent properties, can be used as a soak for exudative eczematous areas (section 13.5.1); treatment should be stopped when the skin becomes dry. Potassium permanganate can stain skin and nails especially with prolonged use.

13.11.1 Alcohols and saline

ALCOHOL

Cautions flammable; avoid broken skin; patients have suffered severe burns when diathermy has been preceded by application of alcoholic skin disinfectants

Contra-indications neonates, see section 13.1

Indications and dose**Skin preparation before injection**

Apply to skin as necessary

Industrial Methylated Spirit, BP

Solution, 19 volumes of ethanol and 1 volume approved wood naphtha, net price '66 OP' (containing 95% by volume alcohol) 100 mL = 39p; '74 OP' (containing 99% by volume alcohol) 100 mL = 39p. Label: 15

Surgical Spirit, BP

Spirit, methyl salicylate 0.5 mL, diethyl phthalate 2%, castor oil 2.5%, in industrial methylated spirit, net price 100 mL = 20p. Label: 15

SODIUM CHLORIDE

Indications and dose

See notes above

Nebuliser diluent section 3.1.5

Sodium depletion section 9.2.1.2

Electrolyte imbalance section 9.2.2.1

Eye section 11.8.1

Oral hygiene section 12.3.4

Sodium Chloride (Non-proprietary)

Solution (sterile), sodium chloride 0.9%, net price 25 × 20-mL unit = £4.95, 200-mL can = £2.65, 1 litre = 80p

Flowfusor® (Fresenius Kabi)

Solution (sterile), sodium chloride 0.9%, net price 120-mL Bellows Pack = £1.53

Irriclen® (ConvaTec)

Solution in aerosol can (sterile), sodium chloride 0.9%, net price 240-mL can = £3.46

Irripod® (C D Medical)

Solution (sterile), sodium chloride 0.9%, net price 25 × 20-mL sachet = £5.84

Miniversol® (Aguettant)

Solution (sterile), sodium chloride 0.9%, net price 30 × 45-mL unit = £13.20; 30 × 100-mL unit = £19.50

Normasol® (Mölnlycke)

Solution (sterile), sodium chloride 0.9%, net price 25 × 25-mL sachet = £6.36; 10 × 100-mL sachet = £7.73

Stericlen® (C D Medical)

Solution in aerosol can (sterile), sodium chloride 0.9%, net price 100-mL can = £2.06, 240-mL can = £3.13

Steripod® Sodium Chloride (Medlock)

Solution (sterile), sodium chloride 0.9%, net price 25 × 20-mL sachet = £7.84

13.11.2 Chlorhexidine salts

CHLORHEXIDINE

Cautions avoid contact with eyes, brain, meninges and middle ear; not for use in body cavities; alcoholic solutions not suitable before diathermy or for use on neonatal skin

Side-effects occasional sensitivity

Indications and dose

See under preparations

Bladder irrigation and catheter patency solutions section 7.4.4**Chlorhexidine 0.05%** (Baxter)

2000 Solution (sterile), pink, chlorhexidine acetate 0.05%, net price 1000 mL = £0.77
For cleansing and disinfecting wounds and burns

Cepton® (LPC)

Skin wash (= solution), red, chlorhexidine gluconate 1%, net price 150 mL = £3.64
For use as skin wash in acne

Lotion, blue, chlorhexidine gluconate 0.1%, net price 150 mL = £2.48
For skin disinfection in acne

Chloraprep® (CareFusion)

Cutaneous solution, sterile, chlorhexidine gluconate 2% in isopropyl alcohol 70%, net price (all with single applicator) 0.67 mL (with **SEPP**® applicator) = 30p, 1.5 mL (with **FREPP**® applicator) = 55p, 1.5 mL = 55p, 3 mL = 85p, 10.5 mL = £2.92, 26 mL = £6.50; (all with single applicator, with tint) 3 mL = 89p, 10.5 mL = £3.07, 26 mL = £6.83
For skin disinfection before invasive procedures; **Child under 2 months** not recommended
Note Flammable

CX Antiseptic Dusting Powder® (Ecolab)

Dusting powder, sterile, chlorhexidine acetate 1%, net price 15 g = £3.93
For skin disinfection

Hibiscrub® (Mölnlycke)

Cleansing solution, red, chlorhexidine gluconate 4%, perfumed, in a surfactant solution, net price 250 mL = £4.25, 500 mL = £5.25, 5 litres = £24.00
Excipients include fragrance
Use instead of soap for pre-operative hand and skin preparation and for general hand and skin disinfection

Hibi® Liquid Hand Rub+ (Mölnlycke)

Solution, chlorhexidine gluconate 0.5%, in isopropyl alcohol 70% with emollients, net price 500 mL = £5.25
To be used undiluted for hand and skin disinfection

Hibitane Obstetric® (Derma UK)

Cream, chlorhexidine gluconate solution 5% (= 1% chlorhexidine gluconate), in a pourable water-miscible basis, net price 250 mL = £9.00
For use in obstetrics and gynaecology as an antiseptic and lubricant (for application to skin around vulva and perineum and to hands of midwife or doctor)

Hydrex® (Ecolab)

Solution, chlorhexidine gluconate solution 2.5% (= chlorhexidine gluconate 0.5%), in denatured ethanol 70%, net price 600 mL (clear) = £3.49; 600 mL (pink) = £3.49, 200-mL spray = £1.77, 500-mL spray = £3.01
Note Flammable
For pre-operative skin disinfection

Surgical scrub, chlorhexidine gluconate 4% in a surfactant solution, net price 250 mL = £3.39, 500 mL = £3.59

Excipients include fragrance

For pre-operative hand and skin preparation and for general hand disinfection

Unisept® (Medlock)

Solution (sterile), pink, chlorhexidine gluconate 0.05%, net price 25 × 25-mL sachet = £5.54; 10 × 100-mL sachet = £6.83

To be used undiluted for general skin disinfection and swabbing in obstetrics

■ With cetrimide

Tisept® (Medlock)

Solution (sterile), yellow, chlorhexidine gluconate 0.015%, cetrimide 0.15%, net price 25 × 25-mL sachet = £5.33; 10 × 100-mL sachet = £6.85

To be used undiluted for general skin disinfection and wound cleansing

Travasept 100® (Baxter)

Solution (sterile), yellow, chlorhexidine acetate 0.015%, cetrimide 0.15%, net price 500 mL = 72p, 1 litre = 77p

To be used undiluted in skin disinfection such as wound cleansing and obstetrics

Concentrates

Hibitane® Plus 5% Concentrate (Mölnlycke)

Solution, red, chlorhexidine gluconate 5%, in a perfumed aqueous solution, net price 5 litres = £14.50

Dose

Pre-operative skin preparation

Dilute 1 in 10 (0.5%) with alcohol 70%

General skin disinfection

Dilute 1 in 100 (0.05%) with water

Note Alcoholic solutions not suitable for use before diathermy (see Alcohol, p. 600) or on neonatal skin

13.11.3 Cationic surfactants and soaps

CETRIMIDE

Cautions avoid contact with eyes; avoid use in body cavities

Side-effects skin irritation and occasionally sensitisation

Indications and dose

Skin disinfection

■ Preparations

Ingredient of *Tisept®* and *Travasept® 100*, see above

13.11.4 Iodine

POVIDONE-IODINE

Cautions broken skin (see below)

Large open wounds The application of povidone-iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis, hypernatraemia, and impairment of renal function

Contra-indications corrected gestational age under 32 weeks; infants body-weight under 1.5 kg; regular use in neonates; thyroid disorders; concomitant lithium treatment

Renal impairment avoid regular application to inflamed or broken skin or mucosa

Pregnancy sufficient iodine may be absorbed to affect the fetal thyroid in the second and third trimester

Breast-feeding avoid regular or excessive use

Side-effects rarely sensitivity; may interfere with thyroid function tests

Indications and dose

Skin disinfection see preparations

Betadine® (Ayrton Saunders)

Dry powder spray, povidone-iodine 2.5% in a pressurised aerosol unit, net price 150-g unit = £2.63

For skin disinfection, particularly minor wounds and infections; **Child under 2 years** not recommended

Note Not for use in serous cavities

Savlon® Dry (Novartis Consumer Health)

Powder spray, povidone-iodine 1.14% in a pressurised aerosol unit, net price 50-mL unit = £2.51

For minor wounds

Videne® (Ecolab)

Alcoholic tincture, povidone-iodine 10%, net price 500 mL = £5.43

Dose

Apply undiluted in pre-operative skin disinfection

Note Flammable—caution in procedures involving hot wire cautery and diathermy; avoid use in neonates

Antiseptic solution, povidone-iodine 10% in aqueous solution, net price 500 mL = £5.43

Dose

Apply undiluted in pre-operative skin disinfection and general antiseptics

Surgical scrub, povidone-iodine 7.5% in aqueous solution, net price 500 mL = £5.43

Dose

Use as a pre-operative scrub for hand and skin disinfection

13.11.5 Phenolics

Triclosan has been used for disinfection of the hands and wounds, and for disinfection of the skin before surgery.

13.11.6 Oxidisers and dyes

HYDROGEN PEROXIDE

Cautions large or deep wounds; avoid on healthy skin and eyes; bleaches fabric; incompatible with products containing iodine or potassium permanganate

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose

Superficial bacterial skin infection see under preparation below

Crystacide® (Derma UK)

Cream, hydrogen peroxide 1%, net price 25 g = £8.07, 40 g = £11.62

Excipients include edetic acid (EDTA), propylene glycol

Dose**Superficial bacterial skin infection**

Apply 2–3 times daily for up to 3 weeks

POTASSIUM PERMANGANATE

Cautions irritant to mucous membranes

Indications and dose**Cleansing and deodorising suppurating eczematous reactions (section 13.5.1) and wounds**

For wet dressings or baths, use approx. 0.01% (1 in 10 000) solution

Note Stains skin and clothing

Potassium Permanganate Solution

Solution, potassium permanganate 0.1% (1 in 1000) in water

Note to be diluted 1 in 10 to provide a 0.01% (1 in 10 000) solution

Permitabs® (Alliance)

Solution tablets, for preparation of topical solution, potassium permanganate 400 mg, net price 30-tab pack = £14.59

Note 1 tablet dissolved in 4 litres of water provides a 0.01% (1 in 10 000) solution

13.11.7 Desloughing agents

Alginate, hydrogel, and hydrocolloid dressings (see BNF Appendix 5) are effective in wound debridement. Sterile larvae (maggots) (available from BioMonde) are also used for managing sloughing wounds and are prescribable on the NHS.

Desloughing solutions and creams are of little clinical value. Substances applied to an open area are easily absorbed and perilesional skin is easily sensitised.

For further information on wound management products and elastic hosiery, see BNF Appendix 5.

13.12 Antiperspirants

Aluminium chloride is a potent antiperspirant used in the treatment of axillary, palmar, and plantar hyperhidrosis. Aluminium salts are also incorporated in preparations used for minor fungal skin infections associated with hyperhidrosis.

In more severe cases specialists use tap water or **glycopyrronium bromide** (as a 0.05% solution) in the iontophoretic treatment of hyperhidrosis of palms and soles.

Botox® contains botulinum toxin type A complex (section 4.9.3) and is available for use intradermally for severe hyperhidrosis of the axillae unresponsive to topical antiperspirant or other antihidrotic treatment; intradermal treatment is unlikely to be tolerated by most children and should be administered under hospital specialist supervision.

ALUMINIUM SALTS

Cautions avoid contact with eyes or mucous membranes; avoid use on broken or irritated skin; do not shave axillae or use depilatories within 12 hours of application; avoid contact with clothing

Side-effects skin irritation

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose**Hyperhidrosis affecting axillae, hands or feet**

Apply liquid formulation at night to dry skin, wash off the following morning, initially apply daily then reduce frequency as condition improves—do not bathe immediately before use

Hyperhidrosis, bromidrosis, intertrigo, and prevention of tinea pedis and related conditions

Apply powder to dry skin

Anhydrol® Forte (Dermal)

Solution (= application), aluminium chloride hexahydrate 20% in an alcoholic basis, net price 60-mL bottle with roll-on applicator = £2.51. Label: 15

Excipients none as listed in section 13.1.3

Driclor® (Stiefel)

Application, aluminium chloride hexahydrate 20% in an alcoholic basis, net price 75-mL bottle with roll-on applicator = £3.01. Label: 15

Excipients none as listed in section 13.1.3

Note A 30-mL pack is on sale to the public

ZeaSORB® (Stiefel)

Dusting powder, aldioxa 0.22%, chloroxylenol 0.5%, net price 50 g = £2.61

Excipients include fragrance

GLYCOPYRRONIUM BROMIDE

Cautions see notes (Antimuscarinics) in section 1.2 (but poorly absorbed and systemic effects unlikely)

Contra-indications see notes (Antimuscarinics) in section 1.2 (but poorly absorbed and systemic effects unlikely); also infections affecting the treatment site

Side-effects see notes (Antimuscarinics) in section 1.2 (but poorly absorbed and systemic effects unlikely); also tingling at administration site

Licensed use licensed for use in children (age range not specified by manufacturer)

Indications and dose**Iontophoretic treatment of hyperhidrosis**

Consult product literature; only 1 site to be treated at a time, max. 2 sites treated in any 24 hours, treatment not to be repeated within 7 days

Other indications section 15.1.3

Robinul® (AMCo) (PoM)

Powder, glycopyrronium bromide, net price 3 g = £266.00

13.13 Topical circulatory preparations

These preparations are used to improve circulation in conditions such as bruising and superficial thrombophlebitis but are of little value. First aid measures such

as rest, ice, compression, and elevation should be used. Topical preparations containing heparinoids should not be used on large areas of skin, broken or sensitive skin, or mucous membranes. Chilblains are best managed by avoidance of exposure to cold; neither systemic nor topical vasodilator therapy is established as being effective.

Hirudoid® (Genus) 

Cream, heparinoid 0.3% in a vanishing-cream basis, net price 50 g = £3.99

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Dose

Superficial thrombophlebitis, bruising, and haematoma

Child 5–18 years apply up to 4 times daily

Gel, heparinoid 0.3%, net price 50 g = £3.99

Excipients include propylene glycol, fragrance

Dose

Superficial thrombophlebitis, bruising, and haematoma

Child 5–18 years apply up to 4 times daily

14 Immunological products and vaccines

14.1	Active immunity	604
14.2	Passive immunity	607
14.3	Storage and use	607
14.4	Vaccines and antisera	607
14.5	Immunoglobulins	627
14.5.1	Normal Immunoglobulin	628
14.5.2	Disease-specific immunoglobulins	630
14.5.3	Anti-D (Rh ₀) immunoglobulin	632
14.6	International travel	632

14.1 Active immunity

Active immunity can be acquired by natural disease or by vaccination. **Vaccines** stimulate production of antibodies and other components of the immune mechanism; they consist of either:

1. a *live attenuated* form of a virus (e.g. measles, mumps, and rubella vaccine) or bacteria (e.g. BCG vaccine), or
2. *inactivated* preparations of a virus (e.g. influenza vaccine) or bacteria, or
3. *detoxified* exotoxins produced by a micro-organism (e.g. tetanus vaccine), or
4. *extracts* of a micro-organism, which may be derived from the organism (e.g. pneumococcal vaccine) or produced by recombinant DNA technology (e.g. hepatitis B vaccine).

Live attenuated vaccines usually produce durable immunity but not always as long-lasting as that resulting from natural infection.

Inactivated vaccines may require a primary series of injections of vaccine to produce an adequate antibody response, and in most cases booster (reinforcing) injections are required; the duration of immunity varies from months to many years. Some inactivated vaccines are adsorbed onto an adjuvant (such as aluminium hydroxide) to enhance the antibody response.

Advice in this chapter reflects that in the handbook *Immunisation against Infectious Disease* (2006), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI).

Chapters from the handbook are available at www.immunisation.dh.gov.uk

The advice in this chapter also incorporates changes announced by the Chief Medical Officer and Health Department Updates.

Cautions Most children can safely receive the majority of vaccines. Vaccination may be postponed if the child is suffering from an acute illness; however, it is not necessary to postpone immunisation in children with minor illnesses without fever or systemic upset. See also Predisposition to Neurological Problems, below. For individuals with bleeding disorders, see Route of Administration, below. If alcohol or disinfectant is used for cleansing the skin it should be allowed to evaporate before vaccination to prevent possible inactivation of live vaccines.

When 2 or more vaccines are required (and are not available as a combined preparation), they should be given simultaneously at different sites, preferably in a different limb; if more than one injection is to be given in the same limb, they should be administered at least 2.5 cm apart (but see also BCG Vaccines, p. 608). When 2 live vaccines cannot be given at the same time, they should be separated by an interval of at least 4 weeks. For **interactions** see Appendix 1 (vaccines).

See also Cautions under individual vaccines.

Contra-indications Vaccines are contra-indicated in children who have a confirmed anaphylactic reaction to a preceding dose of a vaccine containing the same antigens or vaccine component (such as antibacterials in viral vaccines). The presence of the following excipients in vaccines and immunological products has been noted under the relevant entries:

Gelatin	Polymyxin B
Gentamicin	Streptomycin
Kanamycin	Thiomersal
Neomycin	
Penicillins	

Hypersensitivity to egg Children with evidence of previous anaphylactic reaction to egg should not be given tick-borne encephalitis vaccine, and yellow fever vaccine should only be considered under the guidance of a specialist. Children with a history of egg allergy can be immunised with either an egg-free influenza vaccine, if available, or an influenza vaccine with an ovalbumin content less than 120 nanograms/mL (facilities should be available to treat anaphylaxis). If an influenza vaccine containing ovalbumin is being considered in those with a history of anaphylaxis to egg or egg allergy with uncontrolled asthma, these children should be referred to a specialist in hospital. See also Cautions under MMR vaccine.

See also Vaccines and HIV infection, below.

Live vaccines may be contra-indicated temporarily in individuals who are:

- immunosuppressed (see Impaired Immune Response, below);
- pregnant (see Pregnancy and Breast-feeding, below).

See also Contra-indications under individual vaccines.

Impaired immune response Immune response to vaccines may be reduced in immunosuppressed children and there is also a risk of generalised infection with live vaccines. Severely immunosuppressed children should not be given live vaccines (including those with severe primary immunodeficiency). Specialist advice should be sought for children being treated with high doses of corticosteroids (dose equivalents of prednisolone: **children**, 2 mg/kg (or more than 40 mg) daily for at least 1 week or 1 mg/kg daily for 1 month), or other immunosuppressive drugs¹, and for children with malignant conditions undergoing chemotherapy or generalised radiotherapy^{1,2}. However, with the exception of severe combined immunodeficiency, the benefit from rotavirus vaccination is likely to outweigh the risk in other types of immunosuppression; if there is any doubt, advice should be sought from a specialist. For special reference to *HIV infection*, see below.

The Royal College of Paediatrics and Child Health has produced a statement, *Immunisation of the Immunocompromised Child* (2002) (available at www.rcpch.ac.uk).

Pregnancy Live vaccines should not be administered routinely during pregnancy because of the theoretical risk of fetal infection but where there is a significant risk of exposure to disease (e.g. to yellow fever), the need for vaccination usually outweighs any possible risk to the fetus. Termination of pregnancy following inadvertent immunisation is not recommended. There is no evidence of risk from vaccinating pregnant women with inactivated viral or bacterial vaccines or toxoids. For use of specific vaccines during pregnancy, see under individual vaccines.

Breast-feeding Although there is a theoretical risk of live vaccine being present in breast milk, vaccination is not contra-indicated for women who are breast-feeding when there is significant risk of exposure to disease. There is no evidence of risk from vaccinating women who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids. For use of specific vaccines during breast-feeding, see under individual vaccines.

Side-effects Injection of a vaccine may be followed by local reactions such as pain, inflammation, redness, and lymphangitis. An induration or sterile abscess may develop at the injection site. Gastro-intestinal disturbances, fever, headache, irritability, loss of appetite, fatigue, myalgia, and malaise are among the most commonly reported side-effects. Other side-effects include influenza-like symptoms, dizziness, paraesthesia, asthenia, drowsiness, arthralgia, rash, and lymphadenopathy. Hypersensitivity reactions, such as bronchospasm, angioedema, urticaria, and anaphylaxis, are very rare but can be fatal (see section 3.4.3 for management of allergic emergencies).

Oral vaccines, such as cholera, live poliomyelitis, rotavirus, and live typhoid, can also cause gastro-intestinal disturbances such as nausea, vomiting, abdominal pain and cramps, and diarrhoea.

1. Live vaccines should be postponed until at least 3 months after stopping high-dose systemic corticosteroids and at least 6 months after stopping other immunosuppressive drugs or generalised radiotherapy (at least 12 months after discontinuing immunosuppressants following bone-marrow transplantation).
2. Use of normal immunoglobulin should be considered after exposure to measles (see p. 628) and varicella-zoster immunoglobulin considered after exposure to chickenpox or herpes zoster (see p. 631).

See also Predisposition to Neurological Problems, below.

Some vaccines (e.g. poliomyelitis) produce very few reactions, while others (e.g. measles, mumps and rubella) may cause a very mild form of the disease. Occasionally more serious adverse reactions can occur—these should always be reported to the CHM (see Adverse Reactions to Drugs, p. 11).

See also Preterm Birth, p. 606.

Predisposition to neurological problems

When there is a personal or family history of *febrile convulsions*, there is an increased risk of these occurring during fever from any cause including immunisation, but this is not a contra-indication to immunisation. In children who have had a seizure associated with fever without neurological deterioration, immunisation is *recommended*; advice on the *management of fever* (see Post-immunisation Pyrexia in Infants, below) should be given before immunisation. When a child has had a convulsion not associated with fever, and the neurological condition is not deteriorating, immunisation is *recommended*.

Children with stable neurological disorders (e.g. spina bifida, congenital brain abnormality, and peri-natal hypoxic-ischaemic encephalopathy) should be immunised according to the recommended schedule.

When there is a *still evolving neurological problem*, including poorly controlled epilepsy, immunisation should be deferred and the child referred to a specialist. Immunisation is recommended if a cause for the neurological disorder is identified. If a cause is not identified, immunisation should be deferred until the condition is stable.

Post-immunisation pyrexia in infants

The carer should be advised that if pyrexia develops after childhood immunisation and the infant seems distressed, a dose of paracetamol can be given and, if necessary, a second dose can be given 4–6 hours later. Ibuprofen can be used if paracetamol is unsuitable, but if a second dose of ibuprofen is required, it is given 6 hours after the first dose. The carer should be warned to seek medical advice if the pyrexia persists.

For post-immunisation pyrexia in an infant aged 2–3 months, the dose of paracetamol is 60 mg; the dose of ibuprofen is 50 mg (on a doctor's advice). An oral syringe can be obtained from any pharmacy to give the small volume required.

Further information on adverse effects associated with specific vaccines can be found under individual vaccines.

Vaccines and HIV infection HIV-positive children with or without symptoms can receive the following live vaccines:

MMR (but avoid if immunity significantly impaired), varicella-zoster vaccine against chickenpox (but avoid if immunity significantly impaired—consult product literature)², rotavirus;

and the following inactivated vaccines:

anthrax, cholera (oral), diphtheria, haemophilus influenzae type b, hepatitis A, hepatitis B, human

Immunisation schedule

Vaccines for the childhood immunisation schedule should be obtained from **local health organisations** or from ImmForm (www.immform.dh.gov.uk)—not to be prescribed on FP10 (HS21 in Northern Ireland; GP10 in Scotland; WP10 in Wales).

Preterm birth

Babies born preterm should receive all routine immunisations based on their actual date of birth. The risk of apnoea following vaccination is increased in preterm babies, particularly in those born at or before 28 weeks postmenstrual age. If babies at risk of apnoea are in hospital at the time of their first immunisation, they should be monitored for 48 hours after immunisation. If a baby develops apnoea, bradycardia, or desaturation after the first immunisation, the second immunisation should also be given in hospital with similar monitoring. Seroconversion may be unreliable in babies born earlier than 28 weeks' gestation or in babies treated with corticosteroids for chronic lung disease; consideration should be given to testing for antibodies against *Haemophilus influenzae* type b, meningococcal C, and hepatitis B after primary immunisation.

When to immunise (for preterm infants—see note above)	Vaccine given and dose schedule (for details of dose, see under individual vaccines)
Neonates at risk only	<ul style="list-style-type: none"> ● BCG Vaccine See section 14.4, BCG Vaccines ● Hepatitis B Vaccine See section 14.4, Hepatitis B Vaccine
2 months	<ul style="list-style-type: none"> ● Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated), and Haemophilus Type b Conjugate Vaccine (Adsorbed) First dose ● Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) First dose ● Rotavirus vaccine First dose
3 months	<ul style="list-style-type: none"> ● Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated), and Haemophilus Type b Conjugate Vaccine (Adsorbed) Second dose ● Meningococcal Group C Conjugate Vaccine First dose ● Rotavirus vaccine Second dose
4 months	<ul style="list-style-type: none"> ● Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated), and Haemophilus Type b Conjugate Vaccine (Adsorbed) Third dose ● Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) Second dose
12–13 months	<ul style="list-style-type: none"> ● Measles, Mumps and Rubella Vaccine, Live (MMR) First dose ● Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) Single booster dose ● Haemophilus Type b Conjugate Vaccine and Meningococcal Group C Conjugate Vaccine Single booster dose
Between 3 years and 4 months, and 5 years	<ul style="list-style-type: none"> ● Adsorbed Diphtheria [low dose], Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine or Adsorbed Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine Single booster dose Note: Preferably allow interval of at least 3 years after completing primary course ● Measles, Mumps and Rubella Vaccine, Live (MMR) Second dose
12–13 years (females only)	<ul style="list-style-type: none"> ● Human Papillomavirus Vaccine 3 doses; second dose 1 month, and third dose 4–6 months after first dose¹
13–15 years	<ul style="list-style-type: none"> ● Meningococcal Group C Conjugate Vaccine Single booster dose
13–18 years	<ul style="list-style-type: none"> ● Adsorbed Diphtheria [low dose], Tetanus, and Poliomyelitis (Inactivated) Vaccine Single booster dose Note: Can be given at the same time as the booster dose of meningococcal group C conjugate vaccine at 13–15 years of age
During adult life, women of child-bearing age susceptible to rubella	<ul style="list-style-type: none"> ● Measles, Mumps and Rubella Vaccine, Live (MMR) Women of child-bearing age who have not received 2 doses of a rubella-containing vaccine or who do not have a positive antibody test for rubella should be offered rubella immunisation (using the MMR vaccine)—exclude pregnancy before immunisation, but see also section 14.4, Measles, Mumps and Rubella Vaccine

1. The two human papillomavirus vaccines are not interchangeable and one vaccine product should be used for the entire course.

papillomavirus, influenza (injection), meningococcal, pertussis, pneumococcal, poliomyelitis¹, rabies, tetanus, tick-borne encephalitis, typhoid (injection).

HIV-positive children should **not** receive:

BCG, influenza nasal spray (unless stable HIV infection and receiving antiretroviral therapy), typhoid (oral), yellow fever.²

Note The above advice differs from that for other immunocompromised children; Immunisation of HIV-infected Children issued by Children's HIV Association (CHIVA) are available at www.chiva.org.uk

Vaccines and asplenia The following vaccines are recommended for asplenic children or those with splenic dysfunction:

haemophilus influenzae type b; influenza; meningococcal A, C, W135, and Y conjugate; pneumococcal.

For antibiotic prophylaxis in asplenia see p. 259.

Route of administration Vaccines should not be given intravenously. Most vaccines are given by the intramuscular route, although some are given by either the intradermal route, deep subcutaneous route, or oral route. The intramuscular route should not be used in children with **bleeding disorders** such as haemophilia or thrombocytopenia, vaccines usually given by the intramuscular route should be given by deep subcutaneous injection instead.

Note The Department of Health has advised *against the use of jet guns* for vaccination owing to the risk of transmitting blood-borne infections, such as HIV.

High-risk groups

For information on high-risk groups, see section 14.4 under individual vaccines

BCG Vaccines, p. 608

Hepatitis A Vaccine, p. 612

Hepatitis B Vaccine, p. 614

Influenza Vaccine, p. 616

Pneumococcal Vaccines, p. 622

Tetanus Vaccines, p. 625

Children with unknown or incomplete immunisation history

For children born in the UK who present with an inadequate or unknown immunisation history, investigation into immunisations received should be carried out. Outstanding doses should be administered where the routine childhood immunisation schedule has not been completed.

For advice on the immunisation of children coming to the UK, consult the handbook *Immunisation against Infectious Disease* (2006) (available at www.dh.gov.uk)

14.2 Passive immunity

Immunity with immediate protection against certain infective organisms can be obtained by injecting preparations made from the plasma of immune individuals

1. Inactivated poliomyelitis vaccine is now used instead of oral poliomyelitis vaccine for routine immunisation of children.
2. If yellow fever risk is unavoidable, specialist advice should be sought.

with adequate levels of antibody to the disease for which protection is sought (see under Immunoglobulins, section 14.5). The duration of this passive immunity varies according to the dose and the type of immunoglobulin. Passive immunity may last only a few weeks; when necessary, passive immunisation can be repeated.

Antibodies of human origin are usually termed *immunoglobulins*. The term *antisera* is applied to material prepared in animals. Because of serum sickness and other allergic-type reactions that may follow injections of antisera, this therapy has been replaced whenever possible by the use of immunoglobulins. Reactions are theoretically possible after injection of human immunoglobulins, but reports of such reactions are very rare.

14.3 Storage and use

Care must be taken to store all vaccines and other immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. **Refrigerated storage** is usually necessary; many vaccines and immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Vaccines and immunoglobulins should be protected from light. Reconstituted vaccines and opened multi-dose vials must be used within the period recommended in the product literature. Unused vaccines should be disposed of by incineration at a registered disposal contractor.

Particular attention must be paid to instructions on the use of diluents. Vaccines which are liquid suspensions or are reconstituted before use should be adequately mixed to ensure uniformity of the material to be injected.

14.4 Vaccines and antisera

Availability Anthrax and yellow fever vaccines, botulism antitoxin, diphtheria antitoxin, and snake and spider venom antitoxins are available from local designated holding centres.

For antivenom, see Emergency Treatment of Poisoning, p. 33.

Enquiries for vaccines not available commercially can also be made to:

Vaccines and Countermeasures Response Department
Public Health England
Wellington House
133–155 Waterloo Road
London, SE1 8UG
vaccinesupply@phe.gov.uk

In Scotland information about availability of vaccines can be obtained from a Specialist in Pharmaceutical Public Health.

In Wales enquiries for vaccines not commercially available should be directed to:

Welsh Medicines Information Centre
University Hospital of Wales
Cardiff
CF14 4XW
Tel: (029) 2074 2979

In Northern Ireland:

Pharmacy and Medicines Management Centre
Beech House
Antrim Hospital Site
Northern Health and Social Care Trust
Bush Road
Antrim, BT41 2RL
rphs.admin@northerntrust.hscni.net

For further details of availability, see under individual vaccines.

Anthrax vaccine

Anthrax vaccine is rarely required for children. For further information see BNF section 14.4.

BCG vaccines

BCG (*Bacillus Calmette-Guérin*) is a live attenuated strain derived from *Mycobacterium bovis* which stimulates the development of hypersensitivity to *M. tuberculosis*. BCG vaccine should be given intradermally by operators skilled in the technique (see below).

The expected reaction to successful BCG vaccination is induration at the site of injection followed by a local lesion which starts as a papule 2 or more weeks after vaccination; the lesion may ulcerate then subside over several weeks or months, leaving a small flat scar. A dry dressing may be used if the ulcer discharges, but air should **not** be excluded.

All children of 6 years and over being considered for BCG immunisation must first be given a skin test for hypersensitivity to tuberculinoprotein (see under Diagnostic agents, below). A skin test is not necessary for a child under 6 years, provided that the child has not stayed for longer than 3 months in a country with an incidence¹ of tuberculosis greater than 40 per 100 000, the child has not had contact with a person with tuberculosis, and there is no family history of tuberculosis within the last 5 years.

BCG is recommended for the following groups of children if BCG immunisation has not previously been carried out and they are negative for tuberculinoprotein hypersensitivity:

- neonates with a family history of tuberculosis in the last 5 years;
- all neonates and infants (0–12 months) born in areas where the incidence¹ of tuberculosis is greater than 40 per 100 000;
- neonates, infants, and children under 16 years with a parent or grandparent born in a country with an incidence¹ of tuberculosis greater than 40 per 100 000;
- new immigrants aged under 16 years who were born in, or lived for more than 3 months in a country with an incidence¹ of tuberculosis greater than 40 per 100 000;
- new immigrants aged 16–18 years from Sub-Saharan Africa or a country¹ with an incidence of tuberculosis greater than 500 per 100 000;
- contacts of those with active respiratory tuberculosis;

1. List of countries or primary care trusts where the incidence of tuberculosis is greater than 40 cases per 100 000 is available at www.hpa.org.uk

- children under 16 years intending to live with local people for more than 3 months in a country with an incidence¹ of tuberculosis greater than 40 per 100 000 (section 14.6).

BCG vaccine can be given simultaneously with another live vaccine (see also section 14.1), but if they are not given at the same time, an interval of 4 weeks should normally be allowed between them. When BCG is given to infants, there is no need to delay routine primary immunisations. No further vaccination should be given in the arm used for BCG vaccination for at least 3 months because of the risk of regional lymphadenitis.

For advice on chemoprophylaxis against tuberculosis, see section 5.1.9; for treatment of infection following vaccination, seek expert advice.

BACILLUS CALMETTE-GUÉRIN VACCINE

BCG vaccine

Cautions see section 14.1

Contra-indications see section 14.1; also neonate in household contact with known or suspected case of active tuberculosis; generalised septic skin conditions (for children with eczema, lesion-free site should be used)

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects see section 14.1 and notes above; *also* at the injection-site, subcutaneous abscess, prolonged ulceration; *rarely* disseminated complications such as osteitis or osteomyelitis

Indications and dose

Immunisation against tuberculosis

- By intradermal injection

Neonate 0.05 mL

Child 1 month–1 year 0.05 mL

Child 1–18 years 0.1 mL

Intradermal injection technique Skin is stretched between thumb and forefinger and needle (size 25G or 26G) inserted (bevel upwards) for about 3 mm into superficial layers of dermis (almost parallel with surface). Needle should be short with short bevel (can usually be seen through epidermis during insertion). Tense raised blanched bleb showing tips of hair follicles is sign of correct injection; 7 mm bleb = 0.1 mL injection, 3 mm bleb = 0.05 mL injection; if considerable resistance not felt, needle is too deep and should be removed and reinserted before giving more vaccine.

To be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be **avoided**.

■ Intradermal

Bacillus Calmette-Guérin Vaccine (PoM)

BCG Vaccine, Dried/Tub/BCG

Injection, (powder for suspension), freeze-dried preparation of live bacteria of a strain derived from the bacillus of Calmette and Guérin
Available from health organisations or from **ImmForm** (SSI brand, multidose vial with diluent)

Diagnostic agents

The *Mantoux test* is recommended for tuberculin skin testing, but no licensed preparation is currently available. Guidance for healthcare professionals is available at www.dh.gov.uk/immunisation.

In the Mantoux test, the diagnostic dose is administered by intradermal injection of Tuberculin Purified Protein Derivative (PPD).

The *Heaf test* (involving the use of multiple-puncture apparatus) is no longer available.

Note Response to tuberculin may be suppressed by live viral vaccines, viral infection, sarcoidosis, corticosteroid therapy, or immunosuppression due to disease or treatment.

Tuberculin testing should not be carried out within 4 weeks of receiving a live viral vaccine

Two interferon gamma release assay (IGRA) tests are also available as an aid in the diagnosis of tuberculosis infection: *QuantIFERON®-TB Gold* and *T-SPOT®.TB*. Both tests measure T-cell mediated immune response to synthetic antigens. For further information on the use of interferon gamma release assay tests for tuberculosis, see www.hpa.org.uk.

Tuberculin Purified Protein Derivative (PoM) (Tuberculin PPD)

Injection, heat-treated products of growth and lysis of appropriate *Mycobacterium* spp. 20 units/mL (2 units/0.1-mL dose) (for routine use), 1.5-mL vial; 100 units/mL (10 units/0.1-mL dose), 1.5-mL vial

Dose

Mantoux test

• By intradermal injection

2 units (0.1 mL of 20 units/mL strength) for routine Mantoux test; if first test is negative and a further test is considered appropriate 10 units (0.1 mL of 100 units/mL strength)

Available from *ImmForm* (SSI brand)

Important The strength of tuberculin PPD in this product may be different to the strengths of products used previously for the Mantoux test; care is required to select the correct strength

Botulism antitoxin

A polyvalent botulism antitoxin is available for the post-exposure prophylaxis of botulism and for the treatment of children thought to be suffering from botulism. It specifically neutralises the toxins produced by *Clostridium botulinum* types A, B, and E. It is not effective against infantile botulism as the toxin (type A) is seldom, if ever, found in the blood in this type of infection.

Hypersensitivity reactions are a problem. It is essential to read the contra-indications, warnings, and details of sensitivity tests on the package insert. Prior to treatment checks should be made regarding previous administration of any antitoxin and history of any allergic condition, e.g. asthma, hay fever, etc. All children should be tested for sensitivity (diluting the antitoxin if history of allergy).

Botulism Antitoxin (PoM)

A preparation containing the specific antitoxic globulins that have the power of neutralising the toxins formed by types A, B, and E of *Clostridium botulinum*.

Note The BP title Botulinum Antitoxin is not used because the preparation currently in use may have a different specification

Dose

Prophylaxis

Consult product literature

Available from local designated centres, for details see TOXBASE (requires registration) www.toxbase.org. For supplies outside working hours apply to other designated centres or to the Public Health England Colindale duty doctor (Tel (020) 8200 6868). For major incidents, obtain supplies from the local blood bank

Cholera vaccine

Cholera vaccine (oral) contains inactivated Inaba (including El-Tor biotype) and Ogawa strains of *Vibrio cholerae*, serotype O1 together with recombinant B-subunit of the cholera toxin produced in Inaba strains of *V.cholerae*, serotype O1.

Oral cholera vaccine is licensed for travellers to endemic or epidemic areas on the basis of current recommendations (see also section 14.6). Immunisation should be completed at least 1 week before potential exposure. However, there is no requirement for cholera vaccination for international travel.

Immunisation with cholera vaccine does not provide complete protection and all travellers to a country where cholera exists should be warned that scrupulous attention to food, water, and personal hygiene is **essential**.

Injectable cholera vaccine provides unreliable protection and is no longer available in the UK.

CHOLERA VACCINE

Cautions see section 14.1 and notes above

Contra-indications see section 14.1; also acute gastro-intestinal illness

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects see section 14.1; also *rarely* respiratory symptoms such as rhinitis and cough; *very rarely* sore throat, insomnia

Indications and dose

See notes above

• By mouth

Child 2–6 years 3 doses each separated by an interval of 1–6 weeks

Child 6–18 years 2 doses separated by an interval of 1–6 weeks

Note If more than 6 weeks have elapsed between doses, the primary course should be restarted

A single booster dose can be given 2 years after primary course for children 6–18 years, and 6 months after primary course for children 2–6 years. If more than 2 years have elapsed since the last vaccination, the primary course should be repeated

Administration Dissolve effervescent sodium bicarbonate granules in a glassful of water (approximately 150 mL). For child over 6 years, add vaccine suspension to make one dose. For child 2–6 years, discard half (approximately 75 mL) of the solution, then add vaccine suspension to make one dose. Drink within 2 hours. Food, drink and other oral medicines should be avoided for 1 hour before and after vaccination

Dukoral® (Crucell) (PoM)

Oral suspension, for dilution with solution of effervescent sodium bicarbonate granules, heat- and formaldehyde-inactivated Inaba (including El-Tor biotype) and Ogawa strains of *Vibrio cholerae* bacteria and recombinant cholera toxin B-subunit produced in *V. cholerae*, net price 2-dose pack = £23.42. Counselling, administration

Diphtheria Vaccines

Diphtheria vaccines are prepared from the toxin of *Corynebacterium diphtheriae* and adsorption on aluminium hydroxide or aluminium phosphate improves anti-

genicity. The vaccine stimulates the production of the protective antitoxin. The quantity of diphtheria toxoid in a preparation determines whether the vaccine is defined as 'high dose' or 'low dose'. Vaccines containing the higher dose of diphtheria toxoid are used for primary immunisation of children under 10 years of age. Vaccines containing the lower dose of diphtheria toxoid are used for primary immunisation in children over 10 years. Single-antigen diphtheria vaccine is not available and adsorbed diphtheria vaccine is given as a combination product containing other vaccines.

For primary immunisation of children aged between 2 months and 10 years vaccination is recommended usually in the form of 3 doses (separated by 1-month intervals) of diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (see Immunisation schedule, section 14.1). In unimmunised children aged over 10 years the primary course comprises of 3 doses of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine.

A booster dose should be given 3 years after the primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed). Children under 10 years should receive either adsorbed diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine or adsorbed diphtheria [low dose], tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine. Children aged over 10 years should receive adsorbed diphtheria [low dose], tetanus, and poliomyelitis (inactivated) vaccine.

A second booster dose, of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine, should be given 10 years after the previous booster dose (this interval can be reduced to a minimum of 5 years if previous doses were delayed). For children who have been vaccinated following a tetanus-prone wound, see Tetanus vaccines, p. 625.

Travel Children travelling to areas with a risk of diphtheria infection should be fully immunised according to the UK schedule (see also section 14.6). If more than 10 years have lapsed since completion of the UK schedule, a dose of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine should be administered.

Contacts Advice on the management of cases of diphtheria, carriers, contacts and outbreaks must be sought from health protection units. The immunisation history of infected children and their contacts should be determined; those who have been incompletely immunised should complete their immunisation and fully immunised individuals should receive a reinforcing dose. For advice on antibacterial treatment to prevent a secondary case of diphtheria in a non-immune child, see Table 2, section 5.1.

DIPHTHERIA-CONTAINING VACCINES

Cautions see section 14.1; see also individual components of vaccines

Contra-indications see section 14.1; see also individual components of vaccines

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects see section 14.1; also restlessness, sleep disturbances, and unusual crying in infants;

Licensed use *Infanrix-IPV + Hib*® not licensed for use in children over 36 months; *Pediacel*® not licensed in children over 4 years but

Department of Health recommends that these be used for children up to 10 years

Indications and dose

See notes above and under preparations

▲Diphtheria-containing vaccines for children under 10 years

Important For children aged 10 years or over see Diphtheria-containing Vaccines for Children Over 10 Years, p. 611, and see Diphtheria-containing Vaccines for Immunisation of Pregnant Women Against Pertussis, p. 611

Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed) (PoM)

Injection, suspension of diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated poliomyelitis and *Haemophilus influenzae* type b (conjugated to tetanus protein), net price 0.5-mL prefilled syringe = £32.00

Excipients may include neomycin, polymyxin B and streptomycin

Dose

Primary immunisation

- By intramuscular injection

Child 2 months–10 years 3 doses each of 0.5 mL separated by intervals of 1 month; see also notes on booster doses, above

Available as part of childhood immunisation schedule from health organisations or **ImmForm**

Brands include *Pediacel*®

Adsorbed Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (PoM)

Injection, suspension of diphtheria toxoid, tetanus toxoid, acellular pertussis and inactivated poliomyelitis vaccine components adsorbed on a mineral carrier, net price 0.5-mL prefilled syringe = £17.56

Excipients may include neomycin and polymyxin B

Dose

First booster dose

- By intramuscular injection

Child 3–10 years 0.5 mL 3 years after primary immunisation; see also notes on booster doses, above

Available as part of childhood immunisation schedule from health organisations or **ImmForm**

Brands include *Infanrix-IPV*®

Adsorbed Diphtheria [low dose], Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine (PoM)

Injection, suspension of diphtheria toxoid [low dose], tetanus toxoid, acellular pertussis and inactivated poliomyelitis vaccine components adsorbed on a mineral carrier, net price 0.5-mL prefilled syringe = £20.00

Excipients may include neomycin, polymyxin B and streptomycin

Dose

First booster dose

- By intramuscular injection

Child 3–10 years 0.5 mL 3 years after primary immunisation; see also notes on booster doses, above

Available as part of childhood immunisation schedule from health organisations or **ImmForm**

Brands include *Repevax*®

▲ Diphtheria-containing vaccines for children over 10 years

A low dose of diphtheria toxoid is sufficient to recall immunity in older children previously immunised against diphtheria but whose immunity may have diminished with time; it is insufficient to cause serious reactions in a child who is already immune. Preparations containing low dose diphtheria should be used for children over 10 years, both for primary immunisation and booster doses. For immunisation of pregnant women against pertussis see Diphtheria-containing Vaccines for Immunisation of Pregnant Women Against Pertussis, p. 611.

Adsorbed Diphtheria [low dose], Tetanus and Poliomyelitis (Inactivated) Vaccine ^(PoM)

Injection, suspension of diphtheria toxoid [low dose], tetanus toxoid and inactivated poliomyelitis vaccine components adsorbed on a mineral carrier, net price 0.5-mL prefilled syringe = £6.50

Excipients may include neomycin, polymyxin B and streptomycin

Dose

Primary immunisation

● By intramuscular injection

Child 10–18 years 3 doses each of 0.5 mL separated by intervals of 1 month; second booster dose, 0.5 mL given 10 years after first booster dose (may also be used as first booster dose in those over 10 years who have received only 3 previous doses of a diphtheria-containing vaccine); see also notes on booster doses, above

Available as part of childhood schedule from health organisations or **ImmForm**

Brands include *Revaxis*®

▲ Diphtheria-containing vaccines for immunisation of pregnant women against pertussis

For immunisation of children over 10 years against diphtheria see Diphtheria-containing Vaccines for Children Over 10 Years, p. 611

Adsorbed Diphtheria [low dose], Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine ^(PoM)

Injection, suspension of diphtheria toxoid [low dose], tetanus toxoid, acellular pertussis and inactivated poliomyelitis vaccine components adsorbed on a mineral carrier, net price 0.5 mL prefilled syringe = £20.00

Excipients may include neomycin, polymyxin B and streptomycin

Contra-indications section 14.1; see also individual components of vaccine; also contra-indicated in pregnant women with a history of encephalopathy of unknown origin within 7 days of previous immunisation with a pertussis-containing vaccine

Dose

Vaccination of pregnant women against pertussis see p. 621

- By intramuscular injection
0.5 mL as a single dose

Available from **ImmForm**
Brands include *Repevax*®

▲ Diphtheria antitoxin

Diphtheria antitoxin is used for passive immunisation in suspected cases of diphtheria only (without waiting for bacteriological confirmation); tests for hypersensitivity should be first carried out. It is derived from horse serum, and reactions are common after administration; resuscitation facilities should be available immediately.

It is no longer used for prophylaxis because of the risk of hypersensitivity; unimmunised contacts should be promptly investigated and given antibacterial prophylaxis (Table 2, section 5.1) and vaccine (see Contacts above, p. 610).

Diphtheria Antitoxin ^(PoM)

Dip/Ser

Dose

Prophylaxis

Not recommended therefore no dose stated (see notes above)

Treatment

Consult product literature

Available from Centre for Infections (Tel (020) 8200 6868) or in Northern Ireland from Public Health Laboratory, Belfast City Hospital (Tel (028) 9032 9241).

Haemophilus type b conjugate vaccine

Haemophilus influenzae type b (Hib) vaccine is made from capsular polysaccharide; it is conjugated with a protein such as tetanus toxoid to increase immunogenicity, especially in young children. *Haemophilus influenzae* type b vaccine is given in combination with diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine, (see under Diphtheria containing Vaccines) as a component of the primary course of childhood immunisation (see Immunisation schedule, section 14.1). For infants under 1 year, the course consists of 3 doses of a vaccine containing *Haemophilus influenzae* type b component, with an interval of 1 month between doses. A booster dose of *haemophilus influenzae* type b vaccine (combined with meningococcal group C conjugate vaccine) should be given at around 12–13 months of age.

Children 1–10 years who have not been immunised against *Haemophilus influenzae* type b need to receive only 1 dose of the vaccine (combined with meningococcal group C conjugate vaccine). However, if a primary course of immunisation has not been completed, these children should be given 3 doses of diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and *haemophilus* type b conjugate vaccine (adsorbed). The risk of infection falls sharply in older children and the vaccine is not normally required for children over 10 years.

Haemophilus influenzae type b vaccine may be given to those over 10 years who are considered to be at increased risk of invasive *H. influenzae* type b disease (such as those with sickle-cell disease or complement deficiency, or those receiving treatment for malignancy).

Invasive *Haemophilus influenzae* type b disease

After recovery from infection, unimmunised and partially immunised index cases under 10 years of age should complete their age-specific course of immunisation. Previously vaccinated cases under 10 years of age should be given an additional dose of *haemophilus influenzae* type b vaccine (combined with meningococcal group C conjugate vaccine) if Hib antibody concentrations are low or if it is not possible to measure antibody concentrations. Index cases of any age with asplenia or splenic dysfunction should complete their immunisation according to the recommendations

below; fully vaccinated cases with asplenia or splenic dysfunction should be given an additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) if they received their previous dose over 1 year ago.

For use of rifampicin in the prevention of secondary cases of *Haemophilus influenzae* type b disease, see Table 2, section 5.1

Asplenia, splenic dysfunction, or complement deficiency Children diagnosed with asplenia, splenic dysfunction, or complement deficiency at:

- *under 2 years of age* should be vaccinated according to the Immunisation Schedule (section 14.1). The booster dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine), given at 12–13 months of age, should be followed at least 1 month later by one dose of meningococcal A, C, W135, and Y conjugate vaccine. An additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) should be given after the second birthday;
- *over 2 years of age* should receive one dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine), followed 1 month later by one dose of meningococcal A, C, W135, and Y conjugate vaccine.

HAEMOPHILUS TYPE B CONJUGATE VACCINE

Cautions see section 14.1

Contra-indications see section 14.1

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects see section 14.1; also, atopic dermatitis, hypotonia

Licensed use *Menitorix*® is not licensed for use in children over 2 years

Indications and dose

See notes above and under preparation

Primary immunisation, see under Diphtheria-containing vaccines

Menitorix® (GSK) (PoM)

Injection, powder for reconstitution, capsular polysaccharide of *Haemophilus influenzae* type b and capsular polysaccharide of *Neisseria meningitidis* group C (both conjugated to tetanus protein), net price single dose vial (with syringe containing 0.5 mL diluent) = £37.76

Dose

- By intramuscular injection

CHILD 1–10 year 0.5 mL

CHILD over 1 year with asplenia or splenic dysfunction (see notes above), 0.5 mL

Available as part of the childhood immunisation schedule from **ImmForm**

Combined vaccines

See also Diphtheria-containing vaccines

Hepatitis A vaccine

Hepatitis A vaccine is prepared from formaldehyde-inactivated hepatitis A virus grown in human diploid cells.

Immunisation is recommended for:

- residents of homes for those with severe learning difficulties;
- children with haemophilia or other conditions treated with plasma-derived clotting factors;
- children with severe liver disease;
- children travelling to high-risk areas (see p. 632);
- adolescents who are at risk due to their sexual behaviour;
- parenteral drug abusers.

Immunisation should be considered for:

- children with chronic liver disease including chronic hepatitis B or chronic hepatitis C;
- prevention of secondary cases in close contacts of confirmed cases of hepatitis A, within 14 days of exposure to the primary case (within 8 weeks of exposure to the primary case where there is more than 1 contact in the household).

A booster dose of hepatitis A vaccine is usually given 6–12 months after the initial dose. A second booster dose can be given 20 years after the previous booster dose to those who continue to be at risk. Specialist advice should be sought on re-immunisation of immunocompromised individuals.

In children under 16 years, a single dose of the combined vaccine *Ambirix*® can be used to provide rapid protection against hepatitis A.

Intramuscular normal immunoglobulin (section 14.5.1) is recommended for use in addition to Hepatitis A vaccine for close contacts (of confirmed cases of hepatitis A) who have chronic liver disease or HIV infection, or who are immunosuppressed.

Post-exposure prophylaxis is not required for healthy children under 1 year of age, so long as all those involved in nappy changing are vaccinated against hepatitis A. However, children 2–12 months of age can be given a dose of hepatitis A vaccine if it is not possible to vaccinate their carers, or if the child becomes a source of infection to others [unlicensed use]; in these cases, if the child goes on to require long-term protection against hepatitis A after the first birthday, the full course of 2 doses should be given.

HEPATITIS A VACCINE

Cautions section 14.1

Contra-indications section 14.1

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects section 14.1; for combination vaccines, see also Typhoid vaccines, p. 626

Indications and dose

Immunisation against hepatitis A infection

For dose, see under preparations

Single component

Avaxim® (Sanofi Pasteur) (PoM)

Injection, suspension of formaldehyde-inactivated hepatitis A virus (GBM grown in human diploid cells) 320 antigen units/mL adsorbed onto aluminium hydroxide, net price 0.5-mL prefilled syringe = £18.10

Excipients include neomycin
Dose

- By intramuscular injection
(see note below)

Child 16–18 years 0.5 mL as a single dose; booster dose 0.5 mL 6–12 months after initial dose

Note Booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose with *Avaxim*®. The deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for children with bleeding disorders

Epaxal® (Crucell) (PoM)

Injection, suspension of formaldehyde-inactivated hepatitis A virus (RG-SB grown in human diploid cells) at least 48 units/mL, net price 0.5-mL prefilled syringe = £23.81

Dose

- By intramuscular injection
(see note below)

Child 1–18 years 0.5 mL as a single dose; booster dose 0.5 mL 6–12 months after initial dose (1–6 months if splenectomised)

Note Booster dose may be delayed by up to 4 years if not given after recommended interval following primary dose. The deltoid region is the preferred site of injection. The subcutaneous route may be used for children with bleeding disorders

Important *Epaxal*® contains influenza virus haemagglutinin grown in the allantoic cavity of chick embryos, and is therefore contra-indicated in those hypersensitive to eggs or chicken protein.

Havrix Monodose® (GSK) (PoM)

Injection, suspension of formaldehyde-inactivated hepatitis A virus (HM 175 grown in human diploid cells) 1440 ELISA units/mL adsorbed onto aluminium hydroxide, net price 1-mL prefilled syringe = £22.14, 0.5-mL (720 ELISA units) prefilled syringe (*Havrix Junior Monodose*®) = £16.77

Excipients include neomycin
Dose

- By intramuscular injection
(see note below)

Child 1–15 years 0.5 mL as a single dose; booster dose 0.5 mL 6–12 months after initial dose

Child 16–18 years 1 mL as a single dose; booster dose 1 mL 6–12 months after initial dose

Note Booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose with *Havrix Monodose*®. The deltoid region is the preferred site of injection. The subcutaneous route may be used for children with bleeding disorders

Vaqt® Paediatric (Sanofi Pasteur) (PoM)

Injection, suspension of formaldehyde-inactivated hepatitis A virus (grown in human diploid cells) 50 antigen units/mL adsorbed onto aluminium hydroxyphosphate sulfate, net price 0.5-mL prefilled syringe = £14.74

Excipients include neomycin
Dose

- By intramuscular injection
(see note below)

Child 1–18 years 0.5 mL as a single dose; booster dose

0.5 mL 6–18 months after initial dose

Note The deltoid region is the preferred site of injection. The subcutaneous route may be used for children with bleeding disorders (but immune response may be reduced)

With hepatitis B vaccine

Ambirix® (GSK) (PoM)

Injection, suspension of inactivated hepatitis A virus (grown in human diploid cells) 720 ELISA units/mL adsorbed onto aluminium hydroxide, and recombinant (DNA) hepatitis B surface antigen (grown in yeast cells) 20 micrograms/mL adsorbed onto aluminium hydroxide and aluminium phosphate, net price 1-mL prefilled syringe = £31.18

Excipients include neomycin
Dose

- By intramuscular injection
(see note below)

Child 1–15 years primary course, 2 doses of 1 mL, the second 6–12 months after initial dose

Note Primary course should be completed with *Ambirix*® (single component vaccines given at appropriate intervals may be used for booster dose); the deltoid region is the preferred site of injection in older children; anterolateral thigh is the preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced); subcutaneous route used for children with bleeding disorders (but immune response may be reduced)

Important *Ambirix*® not recommended for post-exposure prophylaxis following percutaneous (needle-stick), ocular, or mucous membrane exposure to hepatitis B virus

Twinvix® (GSK) (PoM)

Injection, inactivated hepatitis A virus (grown in human diploid cells) 720 ELISA units/mL adsorbed onto aluminium hydroxide, and recombinant (DNA) hepatitis B surface antigen (grown in yeast cells) 20 micrograms/mL adsorbed onto aluminium phosphate, net price 1-mL prefilled syringe (*Twinvix*® *Adult*) = £27.76, 1-mL vial (*Twinvix*® *Adult*) = £26.44, 0.5-mL prefilled syringe (*Twinvix*® *Paediatric*) = £20.79

Excipients include neomycin
Dose

- By intramuscular injection
(see note below)

Child 1–15 years primary course 3 doses of 0.5 mL (*Twinvix*® *Paediatric*), the second 1 month and the third 6 months after first dose

Child 16–18 years primary course, 3 doses of 1 mL (*Twinvix*® *Adult*), the second 1 month and the third 6 months after first dose

Accelerated schedule (e.g. for travellers departing within 1 month) for child over 16 years, second dose given 7 days after first dose, third dose after further 14 days and fourth dose 12 months after the first dose

Note Primary course should be completed with *Twinvix*® (single component vaccines given at appropriate intervals may be used for booster dose); the deltoid region is the preferred site of injection in older children; anterolateral thigh is the preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced); subcutaneous route used for children with bleeding disorders (but immune response may be reduced).

Important *Twinvix*® not recommended for post-exposure prophylaxis following percutaneous (needle-stick), ocular or mucous membrane exposure to hepatitis B virus.

With typhoid vaccine

Hepatitis B (GSK) (PoM)

Injection, suspension of inactivated hepatitis A virus (grown in human diploid cells) 1440 ELISA units/mL adsorbed onto aluminium hydroxide, combined with typhoid vaccine containing 25 micrograms/mL virulence polysaccharide antigen of *Salmonella typhi*, net price 1-mL prefilled syringe = £32.08

Excipients include neomycin

Note May be difficult to obtain

Dose

- By intramuscular injection (see note below)

Child 15–18 years 1 mL as a single dose; booster doses, see under single component hepatitis A vaccine (above) and under polysaccharide typhoid vaccine, p. 626

Note The deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for children with bleeding disorders

VIATIM® (Sanofi Pasteur) (PoM)

Injection, suspension of inactivated hepatitis A virus (grown in human diploid cells) 160 antigen units/mL adsorbed onto aluminium hydroxide, combined with typhoid vaccine containing 25 micrograms/mL virulence polysaccharide antigen of *Salmonella typhi*, net price 1-mL prefilled syringe = £29.80

Dose

- By intramuscular injection (see note below)

Child 16–18 years 1 mL as a single dose; booster doses, see under single component hepatitis A vaccine (above) and under polysaccharide typhoid vaccine, p. 626

Note The deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for children with bleeding disorders

Hepatitis B vaccine

Hepatitis B vaccine contains inactivated hepatitis B virus surface antigen (HBsAg) adsorbed on to aluminium hydroxide adjuvant. It is made biosynthetically using recombinant DNA technology. The vaccine is used in individuals at high risk of contracting hepatitis B.

In the UK, high-risk groups include:

- parenteral drug misusers, their sexual partners, and household contacts; other drug misusers who are likely to 'progress' to injecting;
- adolescents who are at risk from their sexual behaviour;
- close family contacts of an individual with chronic hepatitis B infection;
- babies whose mothers have had acute hepatitis B during pregnancy or are positive for hepatitis B surface antigen (regardless of e-antigen markers); hepatitis B vaccination is started immediately on delivery and *hepatitis B immunoglobulin* (see p. 630) given at the same time (but at a different site). Babies whose mothers are positive for hepatitis B surface antigen and for e-antigen antibody should receive the vaccine only (but babies weighing 1.5 kg or less should also receive the immunoglobulin regardless of the mother's e-antigen antibody status);
- children with haemophilia, those receiving regular blood transfusions or blood products, and carers responsible for the administration of such products;

- children with chronic renal failure including those on haemodialysis. Children receiving haemodialysis should be monitored for antibodies annually and re-immunised if necessary. Home carers (of dialysis patients) should be vaccinated;
- children with chronic liver disease;
- patients of day-care or residential accommodation for those with severe learning difficulties;
- children in custodial institutions;
- children travelling to areas of high or intermediate prevalence who are at increased risk or who plan to remain there for lengthy periods (see p. 632);
- families adopting children from countries with a high or intermediate prevalence of hepatitis B;
- foster carers and their families.

Different immunisation schedules for hepatitis B vaccine are recommended for specific circumstances (see under individual preparations); an 'accelerated schedule' is recommended for pre-exposure prophylaxis in high-risk groups where rapid protection is required, and for post-exposure prophylaxis (see below). Generally, three or four doses are required for primary immunisation. Immunisation may take up to 6 months to confer adequate protection; the duration of immunity is not known precisely, but a single booster 5 years after the primary course may be sufficient to maintain immunity for those who continue to be at risk.

Immunisation does not eliminate the need for common-sense precautions for avoiding the risk of infection from known carriers by the routes of infection which have been clearly established, consult *Guidance for Clinical Health Care Workers: Protection against Infection with Blood-borne Viruses* (available at www.dh.gov.uk). Accidental inoculation of hepatitis B virus-infected blood into a wound, incision, needle-prick, or abrasion may lead to infection, whereas it is unlikely that indirect exposure to a carrier will do so.

Following significant exposure to hepatitis B, an accelerated schedule, with the second dose given 1 month, and the third dose 2 months after the initial dose, is recommended. For those at continued risk, a fourth dose should be given 12 months after the first dose. More detailed guidance is given in the *Immunisation against Infectious Disease* handbook, see p. 604.

Specific **hepatitis B immunoglobulin** ('HBIG') is available for use with the vaccine in those accidentally inoculated and in neonates at special risk of infection (section 14.5.2).

A combined hepatitis A and hepatitis B vaccine is also available.

HEPATITIS B VACCINE

Cautions section 14.1

Contra-indications section 14.1

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects section 14.1

Indications and dose

Immunisation against hepatitis B infection

For dose see under preparations

Single component

Engerix B® (GSK) (PoM)

Injection, suspension of hepatitis B surface antigen (prepared from yeast cells by recombinant DNA technique) 20 micrograms/mL adsorbed onto aluminium hydroxide, net price 0.5-mL (paediatric) pre-filled syringe = £9.67, 1-mL vial = £12.34, 1-mL pre-filled syringe = £12.99

Dose

- By intramuscular injection (see note below)

Neonate (except if born to hepatitis B surface antigen-positive mother, see below), 3 doses of 10 micrograms, second dose 1 month and third dose 6 months after first dose

Child 1 month–16 years 3 doses of 10 micrograms, second dose 1 month and third dose 6 months after first dose

Child 16–18 years 3 doses of 20 micrograms, second dose 1 month and third dose 6 months after first dose
Accelerated schedule (all age groups), second dose 1 month after first dose, third dose 2 months after first dose and fourth dose 12 months after first dose
Alternative schedule for **Child 11–15 years**, 2 doses of 20 micrograms, the second dose 6 months after the first dose (this schedule not suitable if high risk of infection between doses or if compliance with second dose uncertain)

Infant born to hepatitis B surface antigen-positive mother (see also notes above)

- By intramuscular injection (see note below)

Neonate 4 doses of 10 micrograms, first dose at birth with hepatitis B immunoglobulin injection (separate site) the second 1 month, the third 2 months and the fourth 12 months after first dose

Renal insufficiency (including haemodialysis patients)

- By intramuscular injection (see note below)

Neonate (except if born to hepatitis B surface antigen positive mother, see above), 3 doses of 10 micrograms, second dose 1 month and third dose 6 months after first dose or accelerated schedule, 4 doses of 10 micrograms, second dose 1 month, third dose 2 months, and fourth dose 12 months after first dose; immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration

Child 1 month–16 years 3 doses of 10 micrograms, second dose 1 month and third dose 6 months after first dose or accelerated schedule, 4 doses of 10 micrograms, second dose 1 month, third dose 2 months, and fourth dose 12 months after first dose; immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration

Child 16–18 years 4 doses of 40 micrograms, the second 1 month, the third 2 months and the fourth 6 months after the first dose; immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration

Note Deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in neonates, infants and young children; not to be injected into the buttock (vaccine efficacy reduced)

Fendrix® (GSK) (PoM)

Injection, suspension of hepatitis B surface antigen (prepared from yeast cells by recombinant DNA technique) 40 micrograms/mL adsorbed onto aluminium phosphate, net price 0.5-mL pre-filled syringe = £38.10

Excipients include traces of thiomersal

Dose

Renal insufficiency patients (including pre-haemodialysis and haemodialysis patients)

- By intramuscular injection

(see note below)

Child 15–18 years 4 doses of 20 micrograms, the second 1 month, the third 2 months and the fourth 6 months after the first dose; immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration

Note Deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced)

HBVaxPro® (Sanofi Pasteur) (PoM)

Injection, suspension of hepatitis B surface antigen (prepared from yeast cells by recombinant DNA technique) 10 micrograms/mL adsorbed onto aluminium hydroxyphosphate sulfate, net price 0.5-mL (5-microgram) pre-filled syringe = £8.95, 1-mL (10-microgram) pre-filled syringe = £12.20; 40 micrograms/mL, 1-mL (40-microgram) vial = £27.60

Dose

- By intramuscular injection (see note below)

Neonate (except if born to hepatitis B surface antigen-positive mother, see below), 3 doses of 5 micrograms, second dose 1 month and third dose 6 months after first dose

Child 1 month–16 years 3 doses of 5 micrograms, second dose 1 month and third dose 6 months after first dose

Child 16–18 years 3 doses of 10 micrograms, second dose 1 month and third dose 6 months after first dose
Accelerated schedule (all age groups), second dose 1 month after first dose, third dose 2 months after first dose with fourth dose at 12 months
Booster doses may be required in immunocompromised patients with low antibody concentration

Infant born to hepatitis B surface antigen-positive mother (see also notes above)

- By intramuscular injection (see note below)

Neonate 4 doses of 5 micrograms, first dose at birth with hepatitis B immunoglobulin injection (separate site), the second 1 month, the third 2 months and the fourth 12 months after the first dose

Chronic haemodialysis patients

- By intramuscular injection (see note below)

Child 16–18 years 3 doses of 40 micrograms, second dose 1 month and third dose 6 months after first dose; booster doses may be required in those with low antibody concentration

Note Deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in neonates and infants; not to be injected into the buttock (vaccine efficacy reduced)

With hepatitis A vaccine

See Hepatitis A Vaccine

Human papillomavirus vaccines

Human papillomavirus vaccine is available as a bivalent vaccine (*Cervarix*®) or a quadrivalent vaccine (*Gardasil*®). *Cervarix*® is licensed for use in females for the prevention of cervical cancer and other pre-cancerous lesions caused by human papillomavirus types 16 and 18. *Gardasil*® is licensed for use in females for the prevention of cervical cancer, genital warts and pre-cancerous lesions caused by human papillomavirus types 6, 11, 16 and 18. The vaccines may also provide

limited protection against disease caused by other types of human papillomavirus. The two vaccines are not interchangeable and one vaccine product should be used for an entire course.

Human papillomavirus vaccine will be most effective if given before sexual activity starts. The first dose is given to females aged 12 to 13 years, the second and third doses are given 1 and 4–6 months after the first dose (see Immunisation schedule, section 14.1); all 3 doses should be given within a 12-month period. If the course is interrupted, it should be resumed but not repeated, allowing the appropriate interval between the remaining doses. Where the second dose was given late and there are significant challenges in scheduling vaccination, or a high likelihood that the third dose will not be given, in exceptional circumstances, the third dose can be given at least 1 month after the second dose. Under the national programme in England, females remain eligible to receive the vaccine up to the age of 18 years if they did not receive the vaccine when scheduled. Where appropriate, immunisation with human papillomavirus vaccine should be offered to females coming into the UK as they may not have been offered protection in their country of origin. The duration of protection has not been established, but current studies suggest that protection is maintained for at least 6 years after completion of the primary course.

HUMAN PAPILLOMAVIRUS VACCINES

Cautions see section 14.1

Contra-indications see section 14.1

Pregnancy not known to be harmful, but vaccination should be postponed until completion of pregnancy

Breast-feeding see p. 605

Side-effects see section 14.1

Indications and dose

See notes above and under preparations

Note To avoid confusion, prescribers should specify the brand to be dispensed

Cervarix® (GSK) (PoM)

Injection, suspension of virus-like particles of human papillomavirus type 16 (40 micrograms/mL), type 18 (40 micrograms/mL) capsid protein (prepared by recombinant DNA technique using a Baculovirus expression system) in monophosphoryl lipid A adjuvant adsorbed onto aluminium hydroxide, net price 0.5-mL pre-filled syringe = £80.50

Note To avoid confusion, prescribers should specify the brand to be dispensed

Dose

Prevention of premalignant genital lesions and cervical cancer (see notes above)

- By intramuscular injection into deltoid region

Child 9–18 years 3 doses of 0.5 mL, the second 1 month and the third 6 months after the first dose

Alternative schedule for **Child 9–18 years**, 3 doses of 0.5 mL, the second 1–2.5 months, and the third 5–12 months after the first dose

Gardasil® (Sanofi Pasteur) (PoM)

Injection, suspension of virus-like particles of human papillomavirus type 6 (40 micrograms/mL), type 11 (80 micrograms/mL), type 16 (80 micrograms/mL), type 18 (40 micrograms/mL) capsid protein (prepared from yeast cells by recombinant DNA technique)

adsorbed onto aluminium hydroxyphosphate sulfate, net price 0.5-mL pre-filled syringe = £86.50

Note To avoid confusion, prescribers should specify the brand to be dispensed

Dose

Prevention of premalignant genital lesions, cervical cancer and genital warts (see notes above)

- By intramuscular injection preferably into deltoid region or higher anterolateral thigh

Child 9–18 years 3 doses of 0.5 mL, the second at least 1 month after the first dose and the third at least 3 months after the second dose; schedule should be completed within 12 months

Alternative schedule for **Child 9–13 years**, 2 doses of 0.5 mL, the second 6 months after the first dose (if administered earlier than 6 months, a third dose should be administered)

Influenza vaccine

While most viruses are antigenically stable, the influenza viruses A and B (especially A) are constantly altering their antigenic structure as indicated by changes in the haemagglutinins (H) and neuraminidases (N) on the surface of the viruses. It is essential that influenza vaccines in use contain the H and N components of the prevalent strain or strains recommended each year by the World Health Organization.

Seasonal influenza vaccines will not control epidemics — immunisation is recommended for *persons at high risk*, and to reduce transmission of infection. Annual immunisation is strongly recommended for children (including infants that were preterm or low birth-weight) aged over 6 months with the following conditions:

- chronic respiratory disease (includes asthma treated with continuous or repeated use of inhaled or systemic corticosteroids or asthma with previous exacerbations requiring hospital admission);
- chronic heart disease;
- chronic liver disease;
- chronic renal disease;
- chronic neurological disease;
- diabetes mellitus;
- immunosuppression because of disease (including asplenia or splenic dysfunction) or treatment (including prolonged systemic corticosteroid treatment [for over 1 month at dose equivalents of prednisolone: *child under 20 kg*, 1 mg/kg or more daily; *child over 20 kg*, 20 mg or more daily] and chemotherapy);
- HIV infection (regardless of immune status).

Seasonal influenza vaccine is also recommended for all pregnant women, for children living in long-stay facilities, and for carers of children whose welfare may be at risk if the carer falls ill. Influenza immunisation should also be considered for household contacts of immunocompromised individuals.

From 1 September 2013, seasonal influenza vaccine will also be offered to all children aged 2–4 years (i.e. those born between 2 September 2009 and 1 September 2011). Unless contra-indicated, the live influenza vaccine, *Fluenz®*, is preferred in children aged 2–18 years because it provides a higher level of protection than inactivated influenza vaccine.

Further information on pandemic influenza, avian influenza, and swine influenza may be found at www.dh.gov.uk/pandemicflu and at www.hpa.gov.uk.

INFLUENZA VACCINES

Cautions see section 14.1; increased risk of fever in child under 5 years with *Viroflu*[®] and *Inflexal*[®] V, and in child 5–9 years with *Enzira*[®] or preparations marketed by Pfizer or CSL Biotherapies

Contra-indications see section 14.1 and also under *Fluenz*[®] below; avoid *Enzira*[®] or preparations marketed by Pfizer or CSL Biotherapies in child under 5 years—increased risk of febrile convulsions

Pregnancy see section 14.1; inactivated vaccines not known to be harmful; avoid *Fluenz*[®]

Breast-feeding see section 14.1; inactivated vaccines not known to be harmful; avoid *Fluenz*[®]

Side-effects see section 14.1; also reported, febrile convulsions and transient thrombocytopenia; with intranasal spray, rhinorrhoea

Licensed use Inactivated Influenza Vaccine (Surface Antigen) and *Fluvirin*[®] are not licensed for use in children under 4 years; *Fluarix Tetra*[®] not licensed for use in children under 3 years

Indications and dose

Annual immunisation against seasonal influenza

- By intramuscular injection

Child 6 months–9 years 0.5 mL (repeated after at least 4 weeks in children who have not received seasonal influenza vaccine previously)

Child 9–18 years 0.5 mL as a single dose

- Intranasally

See under *Fluenz*[®] below

▲ Trivalent seasonal influenza vaccines for intramuscular use

Inactivated Influenza Vaccine (Split Virion) (PoM)

Flu

Injection, suspension of formaldehyde-inactivated influenza virus (split virion) grown in fertilised hens' eggs, net price 0.25-mL prefilled syringe = £6.29, 0.5-mL prefilled syringe = £6.59

Excipients may include neomycin and polymyxin B Available from Sanofi Pasteur

Cautions increased risk of fever in child 5–9 years with preparations marketed by Pfizer or CSL Biotherapies—use alternative influenza vaccine if available

Contra-indications avoid preparations marketed by Pfizer or CSL Biotherapies in child under 5 years—increased risk of febrile convulsions

Inactivated Influenza Vaccine (Surface

Antigen) (PoM)

Flu or Flu(adj)

Injection, suspension of propiolactone-inactivated influenza virus (surface antigen) grown in fertilised hens' eggs, net price 0.5-mL prefilled syringe = £4.15

Excipients may include neomycin, polymyxin B and traces of thiomersal

Available from Novartis Vaccines

Agrippal[®] (Novartis Vaccines) (PoM)

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen) grown in fertilised hens' eggs, net price 0.5-mL prefilled syringe = £5.85

Excipients include kanamycin and neomycin

Enzira[®] (Pfizer) (PoM)

Injection, suspension of inactivated influenza virus (split virion) grown in fertilised hens' eggs, net price 0.5-mL prefilled syringe = £5.25

Excipients include neomycin and polymyxin B

Cautions child 5–9 years (increased risk of fever)—use alternative influenza vaccine if available

Contra-indications child under 5 years—increased risk of febrile convulsions

Fluarix[®] (GSK) (PoM)

Injection, suspension of formaldehyde-inactivated influenza virus (split virion) grown in fertilised hens' eggs, net price 0.5-mL prefilled syringe = £5.39

Excipients include gentamicin

Note Ovalbumin content less than 100 nanograms/mL

Fluvirin[®] (Novartis Vaccines) (PoM)

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen) grown in fertilised hens' eggs, net price 0.5 mL prefilled syringe = £5.55

Excipients include neomycin, polymyxin B, and traces of thiomersal

Imuvac[®] (Abbott Healthcare) (PoM)

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen) grown in fertilised hens' eggs, net price 0.5-mL prefilled syringe = £6.59

Excipients include gentamicin

Influvac Desu[®] (Abbott Healthcare) (PoM)

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen, grown in fertilised hens' eggs), net price 0.5-mL prefilled syringe = £5.22

Excipients include gentamicin

Viroflu[®] (Janssen) (PoM)

Injection, suspension of inactivated influenza virus (surface antigen, virosome) grown in fertilised hens' eggs, net price 0.5-mL prefilled syringe = £6.59

Excipients include neomycin and polymyxin B

Cautions child under 5 years (increased risk of fever)—use only if a safer alternative influenza vaccine is not available

Note Ovalbumin content less than 100 nanograms/mL

Note Also available as *Inflexal*[®] V

▲ Tetravalent seasonal influenza vaccine for intramuscular use

Fluarix Tetra[®] (GSK) ▼ (PoM)

Injection, suspension of formaldehyde-inactivated influenza virus (split virion, grown in fertilised hens' eggs), net price 0.5-mL prefilled syringe = £9.94

Excipients include gentamicin

Note Ovalbumin content less than 100 nanograms/mL

▲ Trivalent seasonal influenza vaccine for intranasal use

Fluenz[®] (AstraZeneca) ▼ (PoM)

Nasal spray, suspension of live, attenuated influenza virus (produced in vero cells and grown in fertilised hens' eggs), net price 0.2 mL nasal applicator = £14.00

Excipients include gelatin and gentamicin

Contra-indications see section 14.1; also severe asthma, active wheezing; avoid close contact with severely immunocompromised patients for 1–2 weeks after vaccination; concomitant use with antiviral therapy for

influenza (avoid antivirals for at least 2 weeks after *Fluenz*[®]; avoid *Fluenz*[®] for at least 48 hours after stopping the antiviral); concomitant use with salicylates in children
Dose

Annual immunisation against seasonal influenza

Child 2–18 years 0.1 mL into each nostril as a single dose; for children 2–9 years in the clinical risk groups, who have not received seasonal influenza vaccine previously, repeat after at least 4 weeks

Japanese encephalitis vaccine

Japanese encephalitis vaccine is indicated for travellers to areas in Asia and the Far East where infection is endemic. The primary immunisation course of 2 doses should be completed at least one week before potential exposure to Japanese encephalitis virus.

Up-to-date information on the risk of Japanese encephalitis in specific countries can be obtained from the National Travel Health Network and Centre (www.nathnac.org).

JAPANESE ENCEPHALITIS VACCINE

Cautions see section 14.1

Contra-indications see section 14.1

Pregnancy although manufacturer advises avoid because of limited information, miscarriage has been associated with Japanese encephalitis virus infection acquired during the first 2 trimesters of pregnancy

Breast-feeding see section 14.1

Side-effects see section 14.1, also *less commonly* cough

Indications and dose

Immunisation against Japanese encephalitis

• By intramuscular injection

Child 2 months–3 years 2 doses of 0.25 mL separated by interval of 28 days

Child 3–18 years 2 doses of 0.5 mL separated by interval of 28 days

Note Deltoid muscle is preferred site of injection; anterolateral thigh is preferred site in infants. The subcutaneous route may be used for children with bleeding disorders see section 14.1

Ixiaro[®] (Novartis Vaccines) ▼ (PoM)

Injection, suspension, inactivated Japanese encephalitis virus (produced in Vero cells), adsorbed onto aluminium hydroxide, net price 0.5-mL (6 micrograms) prefilled syringe = £59.50

Measles vaccine

Measles vaccine has been replaced by a combined live measles, mumps and rubella vaccine (MMR vaccine).

MMR vaccine may be used in the control of outbreaks of measles (see under MMR Vaccine).

Single antigen vaccine

No longer available in the UK

Combined vaccines

See MMR vaccine, p. 618

Measles, Mumps and Rubella (MMR) vaccine

A combined live **measles, mumps, and rubella vaccine** (MMR vaccine) aims to eliminate measles, mumps and rubella (and congenital rubella syndrome).

Every child should receive two doses of MMR vaccine by entry to primary school, unless there is a valid contra-indication (see section 14.1). MMR vaccine should be given irrespective of previous measles, mumps, or rubella infection or vaccination.

The first dose of MMR vaccine is given to children aged 12–13 months. A second dose is given before starting school at 3 years and 4 months–5 years of age (see Immunisation schedule, section 14.1).

Children presenting for pre-school booster who have not received the first dose of MMR vaccine should be given a dose of MMR vaccine followed 3 months later by a second dose.

At school-leaving age or at entry into further education, MMR immunisation should be offered to individuals of both sexes who have not received 2 doses during childhood. In those who have received only a single dose of MMR in childhood, a second dose is recommended to achieve full protection. If 2 doses of MMR vaccine are required, the second dose should be given one month after the initial dose.

MMR vaccine should be used to protect against rubella in *seronegative females of child-bearing age* (see Immunisation schedule, section 14.1). MMR vaccine may also be offered to previously *unimmunised and seronegative post-partum* mothers—vaccination a few days after delivery is important because about 60% of congenital abnormalities from rubella infection occur in babies of mothers who have borne more than one child. Immigrants arriving after the age of school immunisation are particularly likely to require immunisation.

Contacts MMR vaccine may also be used in the control of outbreaks of measles and should be offered to susceptible children, including babies, aged over 6 months who are contacts of a case, within 3 days of exposure to infection. Children immunised before 12 months of age should still receive two doses of MMR vaccine at the recommended ages. If one dose of MMR vaccine has already been given to a child, then the second dose may be brought forward to at least one month after the first, to ensure complete protection. If the child is under 18 months of age and the second dose is given within 3 months of the first, then the routine dose before starting school at 3 years and 4 months–5 years should still be given. Children aged under 9 months for whom avoidance of measles infection is particularly important (such as those with history of recent severe illness) can be given normal immunoglobulin (section 14.5, p. 628) after exposure to measles; routine MMR immunisation should then be given after at least 3 months at the appropriate age.

MMR vaccine is **not suitable** for prophylaxis following exposure to mumps or rubella since the antibody response to the mumps and rubella components is too slow for effective prophylaxis.

Children with impaired immune response should not receive live vaccines (for advice on HIV see section 14.1). If they have been exposed to measles infection they should be given normal immunoglobulin (section 14.5).

Travel Unimmunised children over 6 months of age travelling to areas where measles is endemic or epidemic should receive MMR vaccine. Children immunised before 12 months of age should still receive two doses of MMR vaccine at the recommended ages. If one dose of MMR vaccine has already been given to a child,

then the second dose should be brought forward to at least one month after the first, to ensure complete protection. If the child is under 18 months of age and the second dose is given within 3 months of the first, then the routine dose before starting school at 3 years and 4 months–5 years, should still be given.

Side-effects See section 14.1. Also malaise, fever, or a rash can occur after the first dose of MMR vaccine, most commonly about a week after vaccination and lasting about 2 to 3 days. Leaflets are available for parents on advice for reducing fever (including the use of paracetamol). Febrile seizures occur rarely 6 to 11 days after MMR vaccination; the incidence of febrile seizures is lower than that following measles infection. Parotid swelling occurs occasionally, usually in the third week, and rarely, arthropathy 2 to 3 weeks after immunisation. Adverse reactions are considerably less frequent after the second dose of MMR vaccine than after the first dose.

Idiopathic thrombocytopenic purpura has occurred rarely following MMR vaccination, usually within 6 weeks of the first dose. The risk of idiopathic thrombocytopenic purpura after MMR vaccine is much less than the risk after infection with wild measles or rubella virus. Children who develop idiopathic thrombocytopenic purpura within 6 weeks of the first dose of MMR should undergo serological testing before the second dose is due; if the results suggest incomplete immunity against measles, mumps or rubella then a second dose of MMR is recommended. The Specialist and Reference Microbiology Division, Health Protection Agency offers free serological testing for children who develop idiopathic thrombocytopenic purpura *within 6 weeks* of the first dose of MMR.

Post-vaccination aseptic meningitis was reported (rarely and with complete recovery) following vaccination with MMR vaccine containing Urabe mumps vaccine, which has now been discontinued; no cases have been confirmed in association with the currently used Jeryl Lynn mumps vaccine. Children with post-vaccination symptoms are not infectious.

Reviews undertaken on behalf of the CSM, the Medical Research Council, and the Cochrane Collaboration, have not found any evidence of a link between MMR vaccination and bowel disease or autism. The Chief Medical Officers have advised that the MMR vaccine is the safest and best way to protect children against measles, mumps, and rubella. Information (including fact sheets and a list of references) may be obtained from:
www.dh.gov.uk/immunisation

MEASLES, MUMPS AND RUBELLA VACCINE, LIVE

Cautions see section 14.1; also after immunoglobulin administration or blood transfusion, leave an interval of at least 3 months before MMR immunisation as antibody response to measles component may be reduced

Hypersensitivity to egg MMR vaccine can be given safely even when the child has had an anaphylactic reaction to food containing egg. Dislike of eggs, refusal to eat egg, or confirmed anaphylactic reactions to egg-containing food is not a contra-indication to MMR vaccination. Children with a confirmed anaphylactic reaction to the MMR vaccine should be assessed by a specialist.

Contra-indications see section 14.1

Pregnancy avoid pregnancy for at least 1 month after vaccination; see also, p. 605

Breast-feeding see p. 605

Side-effects see section 14.1 and notes above; also *less commonly* sleep disturbance, unusual crying in infants, also reported peripheral and optic neuritis.

Licensed use not licensed for use in children under 9 months

Indications and dose

Immunisation against measles, mumps, and rubella

- By intramuscular or deep subcutaneous injection

CHILD 6 months–18 years primary immunisation, 2 doses each of 0.5 mL, see Immunisation schedule, section 14.1, p. 606; see also notes above for use in outbreaks, for contacts of cases, and for travel

Combined vaccines

MMRvaxPro® (Sanofi Pasteur) (PoM)

Injection, powder for reconstitution, live attenuated, measles virus (Enders' Edmonston strain) and mumps virus (Jeryl Lynn [Level B] strain) prepared in chick embryo cells, and rubella virus (Wistar RA 27/3 strain); single-dose vial (with syringe containing solvent)

Excipients include gelatin and neomycin

Only available as part of childhood immunisation schedule from health organisations or **ImmForm**

Priorix® (GSK) (PoM)

Injection, powder for reconstitution, live attenuated, measles virus (Schwarz strain) and mumps virus (RIT 4385 strain) prepared in chick embryo cells, and rubella virus (Wistar RA 27/3 strain), net price single-dose vial (with syringe containing solvent) = £7.64

Excipients include neomycin

Also available as part of childhood immunisation schedule from health organisations or **ImmForm**

Meningococcal vaccines

Almost all childhood meningococcal disease in the UK is caused by *Neisseria meningitidis* serogroups B and C. **Meningococcal group C conjugate vaccine** protects only against infection by serogroup C. The risk of meningococcal disease declines with age—immunisation is not generally recommended after the age of 25 years.

Tetravalent meningococcal vaccines that cover serogroups A, C, W135, and Y are available. Although the duration of protection has not been established, the meningococcal groups A, C, W135, and Y conjugate vaccine is likely to provide longer-lasting protection than the unconjugated meningococcal polysaccharide vaccine. The antibody response to serogroup C in unconjugated meningococcal polysaccharide vaccines in young children may be suboptimal.

A meningococcal group B vaccine, **Bexsero®**, is licensed in the UK against infection caused by *Neisseria meningitidis* serogroup B. **Bexsero®** contains 3 recombinant *Neisseria meningitidis* serogroup B proteins and the outer membrane vesicles from the NZ 98/254 strain, in order to achieve broad protection against *Neisseria meningitidis* serogroup B; the proteins are adsorbed onto an aluminium compound to stimulate an enhanced immune response.

Childhood immunisation Meningococcal group C conjugate vaccine provides long-term protection against infection by serogroup C of *Neisseria meningitidis*. Immunisation consists of 1 dose given at 3 months of age; 2 booster doses are recommended, the first is given at 12–13 months of age (combined with haemophilus influenzae type b vaccine), and the second at 13–15 years of age (see Immunisation Schedule, section 14.1, p. 606).

Unimmunised children aged 4–12 months should be given 1 dose of meningococcal group C conjugate vaccine and then they should be vaccinated according to the Immunisation Schedule (section 14.1, p. 606). Unimmunised children aged 1–10 years should be given 1 dose of meningococcal group C conjugate vaccine, followed by a booster dose at 13–15 years of age. Unimmunised children aged 10–18 years should be given 1 dose of meningococcal group C conjugate vaccine, but a booster dose is not required.

Children with confirmed serogroup C disease, who have previously been immunised with meningococcal group C vaccine, should be offered meningococcal group C conjugate vaccine before discharge from hospital.

Asplenia, splenic dysfunction, or complement deficiency See p. 612.

Travel Individuals travelling to countries of risk (see below) should be immunised with meningococcal groups A, C, W135, and Y conjugate vaccine, even if they have previously received meningococcal group C conjugate vaccine. If an individual has recently received meningococcal group C conjugate vaccine, an interval of at least 4 weeks should be allowed before administration of the tetravalent (meningococcal groups A, C, W135, and Y) vaccine.

Vaccination is particularly important for those living with local people or visiting an area of risk during outbreaks.

Immunisation recommendations and requirements for visa entry for individual countries should be checked before travelling, particularly to countries in Sub-Saharan Africa, Asia, and the Indian sub-continent where outbreaks and epidemics of meningococcal infection are reported. Country-by-country information is available from the National Travel Health Network and Centre (www.nathnac.org).

Proof of vaccination with the tetravalent (meningococcal groups A, C, W135 and Y) vaccine is required for those travelling to Saudi Arabia during the Hajj and Umrah pilgrimages (where outbreaks of the W135 strain have occurred).

Contacts For advice on the immunisation of laboratory workers and close contacts of cases of meningococcal disease in the UK and on the role of the vaccine in the control of local outbreaks, consult Guidelines for Public Health Management of Meningococcal Disease in the UK at www.hpa.org.uk. See Table 2, section 5.1 for antibacterial prophylaxis for prevention of secondary cases of meningococcal meningitis.

MENINGOCOCCAL VACCINES

Cautions see section 14.1

Contra-indications see section 14.1

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects see section 14.1; also rarely symptoms of meningitis reported (but no evidence that vaccine causes meningococcal C meningitis); also reported in children with meningococcal group B vaccine (*Bexsero*®) unusual crying and rarely Kawasaki disease

Licensed use *Menveo*® not licensed for use in children under 11 years

Indications and dose

Immunisation against *Neisseria meningitidis* for dose, see under preparations

■ Meningococcal group C conjugate vaccine

Menjugate Kit® (Novartis Vaccines) (PoM)

Injection, powder for reconstitution, capsular polysaccharide antigen of *Neisseria meningitidis* group C (conjugated to *Corynebacterium diphtheriae* protein), adsorbed onto aluminium hydroxide, single-dose vials

Dose

- By intramuscular injection

Child 3 months–18 years 0.5 mL, see notes above and Immunisation Schedule, section 14.1

Note Subcutaneous route used for children with bleeding disorders

Available as part of childhood immunisation schedule from **ImmForm**

NeisVac-C® (Baxter) (PoM)

Injection, suspension of polysaccharide antigen of *Neisseria meningitidis* group C (conjugated to tetanus toxoid protein), adsorbed onto aluminium hydroxide, 0.5-mL prefilled syringe

Dose

- By intramuscular injection

Child 3 months–18 years 0.5 mL, see notes above and Immunisation Schedule, section 14.1

Available as part of childhood immunisation schedule from **ImmForm**

■ Meningococcal group C conjugate vaccine with *Haemophilus influenzae* type B vaccine

See *Haemophilus influenzae* type B vaccine

■ Meningococcal groups A, C, W135, and Y conjugate vaccine

Menveo® (Novartis Vaccines) (PoM)

Injection, powder for reconstitution, capsular oligosaccharide antigens of *Neisseria meningitidis* groups A, C, W135, and Y (conjugated to *Corynebacterium diphtheriae* protein), net price single-dose vial (with vial or prefilled syringe containing diluent) = £30.00

Dose

- By intramuscular injection preferably into deltoid region

Child 3 months–1 year 2 doses of 0.5 mL separated by an interval of 1 month

Child 1–18 years 0.5 mL as a single dose

Nimenrix® (GSK) ▼ (PoM)

Injection, powder for reconstitution, capsular polysaccharide antigens of *Neisseria meningitidis* groups A, C, W135, and Y (conjugated to tetanus toxoid protein), net price single-dose vial (with syringe containing diluent) = £30.00

Dose

- By intramuscular injection preferably into deltoid region (or anterolateral thigh in child 1–2 years)

Child 1–18 years 0.5 mL as a single dose; a second dose may be considered after 1 year in those who continue to be at risk of *Neisseria meningitidis* serogroup A infection

■ Meningococcal polysaccharide A, C, W135 and Y vaccine

ACWY Vax[®] (GSK) PoM

Injection, powder for reconstitution, capsular polysaccharide antigens of *Neisseria meningitidis* groups A, C, W135 and Y, net price single-dose vial (with syringe containing diluent) = £16.73

Dose

- By deep subcutaneous injection

Child 5–18 years 0.5 mL as a single dose; booster dose for those at continued risk, 0.5 mL every 5 years

■ Meningococcal group B vaccine

Bexsero[®] (Novartis) PoM

Injection, suspension of antigen of *Neisseria meningitidis* group B (produced in *E. Coli* cells by recombinant DNA technology), adsorbed onto aluminium hydroxide, net price 0.5 mL prefilled syringe = £75.00

Excipients may include traces of kanamycin

Dose

- By deep intramuscular injection preferably into deltoid region (or anterolateral thigh in infants)

Child 2–6 months primary immunisation, 3 doses of 0.5 mL separated by an interval of at least 1 month; booster dose of 0.5 mL given between 1–2 years of age

Child 6 months–1 year (unimmunised) primary immunisation, 2 doses of 0.5 mL separated by an interval of at least 2 months; booster dose of 0.5 mL given between 1–2 years of age and at least 2 months after completion of primary immunisation

Child 1–2 years (unimmunised) primary immunisation, 2 doses of 0.5 mL separated by an interval of at least 2 months; booster dose of 0.5 mL given 12–24 months after completion of primary immunisation

Child 2–11 years (unimmunised) 2 doses of 0.5 mL separated by an interval of at least 2 months

Child 11–18 years (unimmunised) 2 doses of 0.5 mL separated by an interval of at least 1 month

Mumps vaccine

■ Single antigen vaccine

No longer available in the UK

■ Combined vaccines

See MMR Vaccine, p. 618

Pertussis vaccine

Pertussis vaccine is given as a combination preparation containing other vaccines (see Diphtheria Vaccines). Acellular vaccines are derived from highly purified components of *Bordetella pertussis*. Primary immunisation against pertussis (whooping cough) requires 3 doses of an acellular pertussis-containing vaccine (see Immunisation schedule, section 14.1, p. 606), given at intervals of 1 month from the age of 2 months.

All children up to the age of 10 years should receive primary immunisation with diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed).

A booster dose of an acellular pertussis-containing vaccine should ideally be given 3 years after the primary course, although, the interval can be reduced to 1 year if the primary course was delayed.

Children aged 1–10 years who have not received a *pertussis-containing* vaccine as part of their primary immunisation schedule should be offered 1 dose of a suitable pertussis-containing vaccine; after an interval of at least 1 year, a booster dose of a suitable pertussis-containing vaccine should be given. Immunisation against pertussis is not routinely recommended in individuals over 10 years of age.

Vaccination of pregnant women against pertussis

In response to the pertussis outbreak, the UK health departments introduced a temporary programme (October 2012) to vaccinate pregnant women against pertussis, and this programme will continue until further notice. The aim of the programme is to boost the levels of pertussis-specific antibodies that are transferred, through the placenta, from the mother to the fetus, so that the newborn is protected before routine immunisation begins at 2 months of age.

Pregnant women should be offered a single dose of acellular pertussis-containing vaccine (as adsorbed diphtheria [low dose], tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine; *Repevax[®]*) between 28 to 38 weeks of pregnancy; the optimal time for vaccination is between 28–32 weeks of pregnancy. Pregnant women should be offered a single dose of acellular pertussis-containing vaccine up to the onset of labour if they missed the opportunity for vaccination at 28–38 weeks of pregnancy. A single dose of acellular pertussis-containing vaccine may also be offered to new mothers, who have never previously been vaccinated against pertussis, until the child receives the first vaccination.

While this programme is in place, women who become pregnant again should be offered vaccination during each pregnancy to maximise transplacental transfer of antibody.

Contacts Vaccination against pertussis should be considered for close contacts of cases with pertussis who have been offered antibacterial prophylaxis (Table 2, section 5.1). Unimmunised or partially immunised contacts under 10 years of age should complete their vaccination against pertussis. A booster dose of an acellular pertussis-containing vaccine is recommended for contacts aged over 10 years who have not received a pertussis-containing vaccine in the last 5 years and who have not received adsorbed diphtheria [low dose], tetanus, and poliomyelitis (inactivated) vaccine in the last month.

Cautions Section 14.1

Contra-indications Section 14.1

Pregnancy see p. 605

and also Vaccination of Pregnant Women Against Pertussis above

Breast-feeding see p. 605

Side effects See also section 14.1. The incidence of local and systemic effects is generally lower with vaccines containing acellular pertussis components than with the whole-cell pertussis vaccine used. However, compared with primary vaccination, booster doses with vaccines containing acellular pertussis are reported to increase the risk of injection-site reactions (some of which affect the entire limb); local reactions do not contra-indicate further doses (see below).

The vaccine should not be withheld from children with a history to a preceding dose of:

- fever, irrespective of severity;
- persistent crying or screaming for more than 3 hours;
- severe local reaction, irrespective of extent.

Combined vaccines

Combined vaccines, see under Diphtheria vaccines

Pneumococcal vaccines

Pneumococcal vaccines protect against infection with *Streptococcus pneumoniae* (pneumococcus); the vaccines contain polysaccharide from capsular pneumococci, **Pneumococcal polysaccharide vaccine** contains purified polysaccharide from 23 capsular types of pneumococci, whereas **pneumococcal polysaccharide conjugate vaccine** (adsorbed) contains polysaccharide from either 10 capsular types (*Synflorix*®) or 13 capsular types (*Prevenar 13*®) with the polysaccharide being conjugated to protein.

The 13-valent conjugate vaccine is used for childhood immunisation. The recommended schedule consists of 3 doses, the first at 2 months of age, the second at 4 months, and the third at 12–13 months (see Immunisation Schedule, section 14.1).

Pneumococcal vaccination is recommended for individuals at increased risk of pneumococcal infection as follows:

- child under 5 years with a history of invasive pneumococcal disease;
- asplenia or splenic dysfunction (including homozygous sickle cell disease and coeliac disease which could lead to splenic dysfunction);
- chronic respiratory disease (includes asthma treated with continuous or frequent use of a systemic corticosteroid);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- diabetes mellitus;
- immune deficiency because of disease (e.g. HIV infection) or treatment (including prolonged systemic corticosteroid treatment for over 1 month at dose equivalents of prednisolone: *child under 20 kg*, 1 mg/kg or more daily; *child over 20 kg*, 20 mg or more daily);
- presence of cochlear implant;
- conditions where leakage of cerebrospinal fluid could occur.

Where possible, the vaccine should be given at least 2 weeks before splenectomy, cochlear implant surgery, chemotherapy, or radiotherapy; children and carers should be given advice about increased risk of pneumococcal infection. If it is not practical to vaccinate at least 2 weeks before splenectomy, chemotherapy, or radiotherapy, the vaccine should be given at least 2 weeks after the splenectomy or, where possible, at least 3 months after completion of chemotherapy or radiotherapy. Prophylactic antibacterial therapy against pneumococcal infection (Table 2, section 5.1, p. 259) should not be stopped after immunisation. A patient card and

information leaflet for patients with asplenia are available from the Department of Health or in Scotland from the Scottish Executive, Public Health Division 1 (Tel (0131) 244 2501).

Choice of vaccine Children under 2 years at increased risk of pneumococcal infection (see list above) should receive the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) at the recommended ages, followed by a single dose of the 23-valent pneumococcal polysaccharide vaccine after their second birthday (see below). Children at increased risk of pneumococcal infection presenting late for vaccination should receive 2 doses (separated by at least 1 month) of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) before the age of 12 months, and a third dose at 12–13 months. Children over 12 months and under 5 years (who have not been vaccinated or not completed the primary course) should receive a single dose of 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) (2 doses separated by an interval of 2 months in the immunocompromised or those with asplenia or splenic dysfunction). All children under 5 years at increased risk of pneumococcal infection should receive a single dose of the 23-valent pneumococcal polysaccharide vaccine after their second birthday and at least 2 months after the final dose of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed).

Children over 5 years who are at increased risk of pneumococcal disease should receive a single dose of the 23-valent unconjugated pneumococcal polysaccharide vaccine.

Revaccination In individuals with higher concentrations of antibodies to pneumococcal polysaccharides, revaccination with the 23-valent pneumococcal polysaccharide vaccine more commonly produces adverse reactions. Revaccination is therefore not recommended, except every 5 years in individuals in whom the antibody concentration is likely to decline rapidly (e.g. asplenia, splenic dysfunction and nephrotic syndrome). If there is doubt, the need for revaccination should be discussed with a haematologist, immunologist, or microbiologist.

PNEMOCOCCAL VACCINES

Cautions see section 14.1

Contra-indications see section 14.1

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects see section 14.1; *also* Revaccination, above

Indications and dose

Immunisation against pneumococcal infection

For dose see under preparations

■ Pneumococcal polysaccharide vaccines

Pneumovax® II (Sanofi Pasteur) [POM]

Injection, polysaccharide from each of 23 capsular types of pneumococcus, net price 0.5-mL vial = £8.32

Dose

- By subcutaneous or intramuscular injection

Child 2–18 years 0.5 mL; revaccination, see notes above

▲Pneumococcal polysaccharide conjugate vaccine (adsorbed)

Prevenar 13[®] (Pfizer) ▼ [PoM]

Injection, polysaccharide from each of 13 capsular types of pneumococcus (conjugated to carrier protein) adsorbed onto aluminium phosphate, net price 0.5-mL prefilled syringe = £49.10

Dose

- By intramuscular injection

Child 2 months–5 years 0.5 mL (see notes above and Immunisation Schedule, section 14.1)

Note Deltoid muscle is preferred site of injection in young children; anterolateral thigh is preferred site in infants

The dose in *BNF for Children* may differ from that in product literature

Available as part of childhood immunisation schedule from **ImmForm**

Synflorix[®] (GSK) [PoM]

Injection, polysaccharide from each of 10 capsular types of pneumococcus (conjugated to carrier proteins) adsorbed onto aluminium phosphate, net price 0.5-mL prefilled syringe = £27.60

Dose

- By intramuscular injection

Child 6 weeks–5 years consult product literature

Note Deltoid muscle is preferred site of injection in young children; anterolateral thigh is preferred site in infants

Poliomyelitis vaccines

Two types of poliomyelitis vaccine (containing strains of poliovirus types 1, 2, and 3) are available, inactivated poliomyelitis vaccine (for injection) and live (oral) poliomyelitis vaccine. **Inactivated poliomyelitis vaccine**, only available in combined preparation (see under Diphtheria vaccines, combined), is recommended for routine immunisation; it is given by injection and contains inactivated strains of human poliovirus types 1, 2 and 3.

A course of primary immunisation consists of 3 doses of a combined preparation containing inactivated poliomyelitis vaccine starting at 2 months of age with intervals of 1 month between doses (see Immunisation schedule, section 14.1). A course of 3 doses should also be given to all unimmunised children; no child should remain unimmunised against poliomyelitis.

Two booster doses of a preparation containing inactivated poliomyelitis vaccine are recommended, the first before school entry and the second before leaving school (see Immunisation schedule, section 14.1). Further booster doses should be given every 10 years only to individuals at special risk.

Live (oral) poliomyelitis vaccine is no longer available for routine use; its use may be considered during large outbreaks, but advice should be sought from Public Health England. The live (oral) vaccine poses a very rare risk of vaccine-associated paralytic polio because the attenuated strain of the virus can revert to a virulent form. For this reason the live (oral) vaccine must **not** be used for immunosuppressed individuals or their household contacts. The use of inactivated poliomyelitis vaccine removes the risk of vaccine-associated paralytic polio altogether.

Travel Unimmunised travellers to areas with a high incidence of poliomyelitis should receive a full 3-dose course of a preparation containing inactivated poliomyelitis vaccine. Those who have not been vaccinated in the last 10 years should receive a booster dose of

adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine. Information about countries with a high incidence of poliomyelitis can be obtained from www.travax.nhs.uk or from the National Travel Health Network and Centre, p. 633 (www.nathnac.org).

POLIOMYELITIS VACCINES

Cautions see section 14.1

Contra-indications see notes above and section 14.1

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects see notes above and section 14.1

Indications and dose

See under preparations

▲Combined vaccines

See under Diphtheria-containing Vaccines

▲Inactivated (Salk) Vaccine

See under Diphtheria-containing Vaccines

Rabies vaccine

Rabies vaccine contains inactivated rabies virus cultivated in either human diploid cells or purified chick embryo cells; vaccines are used for pre- and post-exposure prophylaxis.

Pre-exposure prophylaxis Immunisation should be offered to children at high risk of exposure to rabies—where there is limited access to prompt medical care for those living in areas where rabies is enzootic, for those travelling to such areas for longer than 1 month, and for those on shorter visits who may be exposed to unusual risk. Transmission of rabies by humans has not been recorded but it is advised that those caring for children with the disease should be vaccinated.

Immunisation against rabies is indicated during pregnancy if there is substantial risk of exposure to rabies and rapid access to post-exposure prophylaxis is likely to be limited.

Up-to-date country-by-country information on the incidence of rabies can be obtained from the National Travel Health Network and Centre (www.nathnac.org) and, in Scotland, from Health Protection Scotland (www.hps.scot.nhs.uk).

Immunisation against rabies requires 3 doses of rabies vaccine, with further booster doses for those who remain at frequent risk.

Post-exposure management Following potential exposure to rabies, the wound or site of exposure (e.g. mucous membrane) should be cleansed under running water and washed for several minutes with soapy water as soon as possible after exposure. Disinfectant and a simple dressing can be applied, but suturing should be delayed because it may increase the risk of introducing rabies virus into the nerves.

Post-exposure prophylaxis against rabies depends on the level of risk in the country, the nature of exposure, and the individual's immunity. In each case, expert risk assessment and advice on appropriate management should be obtained from the local Public Health England Centre or Public Health England's Virus Reference Department, Colindale (tel. (020) 8200 4400) or the PHE Colindale Duty Doctor (tel. (020) 8200 6868), in

Wales from the Public Health Wales local Health Protection Team or Public Health Wales Virus Reference Laboratory (tel. (029) 2074 7747), in Scotland from the local on-call infectious diseases consultant, and in Northern Ireland from the Public Health Agency Duty Room (tel (028) 9055 3997/(028) 9063 2662) or the Regional Virology Service (tel. (028) 9024 0503).

There are no specific contra-indications to the use of rabies vaccine for post-exposure prophylaxis and its use should be considered whenever a child has been attacked by an animal in a country where rabies is enzootic, even if there is no direct evidence of rabies in the attacking animal. Because of the potential consequences of untreated rabies exposure and because rabies vaccination has not been associated with fetal abnormalities, pregnancy is not considered a contra-indication to post-exposure prophylaxis.

For post-exposure prophylaxis of *fully immunised* individuals (who have previously received pre-exposure or post-exposure prophylaxis with cell-derived rabies vaccine), 2 doses of cell-derived vaccine are likely to be sufficient; the first dose is given on day 0 and the second dose is given between day 3–7. Rabies immunoglobulin is not necessary in such cases.

Post-exposure treatment for *unimmunised individuals* (or those whose prophylaxis is possibly incomplete) comprises 5 doses of rabies vaccine given over 1 month (on days 0, 3, 7, 14, and the fifth dose is given between day 28–30); also, depending on the level of risk (determined by factors such as the nature of the bite and the country where it was sustained), rabies immunoglobulin (section 14.5.2) is given to unimmunised individuals on day 0 or within 7 days of starting the course of rabies vaccine. The immunisation course can be discontinued if it is proved that the child was not at risk.

RABIES VACCINE

Cautions see section 14.1

Contra-indications see section 14.1; but see also

Post-exposure Management in notes above

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects see section 14.1; also reported paresis

Indications and dose

Pre-exposure immunisation against rabies

- By intramuscular injection in deltoid region or anterolateral thigh in infants

Child 1 month–18 years 1 mL on days 0, 7, and 28 (3rd dose can be given from day 21 if insufficient time before travel); for those at continuous risk, measure plasma-concentration of antirabies antibodies every 6 months and give a booster dose if the titre is less than 0.5 units/mL; for those at frequent risk, give a single reinforcing dose 1 year after the primary course is completed, and then give booster doses every 3–5 years or determine the frequency of booster doses according to plasma-concentration of antirabies antibodies; for those at infrequent risk, consider giving a booster dose 10 years after the primary course is completed

Post-exposure immunisation against rabies

- By intramuscular injection in deltoid region or anterolateral thigh in infants

Child 1 month–18 years 1 mL (see notes above)

Rabies Vaccine (Sanofi Pasteur) (PoM)

Rab

Injection, powder for reconstitution, freeze-dried inactivated Wistar rabies virus strain PM/WI 38 1503-3M cultivated in human diploid cells, net price single-dose vial with syringe containing diluent = £33.90

Excipients include neomycin

Rabipur® (Novartis Vaccines) (PoM)

Injection, powder for reconstitution, freeze-dried inactivated Flury LEP rabies virus strain cultivated in chick embryo cells, net price single-dose vial = £28.80

Excipients include neomycin

Rotavirus vaccine

Rotavirus vaccine is a live, oral vaccine that protects young children against gastro-enteritis caused by rotavirus infection. The recommended schedule consists of 2 doses, the first at 2 months of age, and the second at 3 months of age (see Immunisation schedule, section 14.1). The first dose of rotavirus vaccine must be given between 6–15 weeks of age and the second dose should be given after an interval of at least 4 weeks; the vaccine should not be started in children 15 weeks of age or older. Ideally, the full course should be completed before 16 weeks of age to provide protection before the main burden of disease, and to avoid a temporal association between vaccination and intussusception; the course must be completed before 24 weeks of age.

The rotavirus vaccine virus is excreted in the stool and may be transmitted to close contacts; however, vaccination of those with *immunosuppressed* close contacts may protect the contacts from wild-type rotavirus disease and outweigh any risk from transmission of vaccine virus. Carers of a recently vaccinated baby should be advised of the need to wash their hands after changing the baby's nappies.

ROTAVIRUS VACCINE

Cautions see section 14.1; *also* diarrhoea or vomiting (postpone vaccination); immunosuppressed close contacts (see notes above)

Contra-indications see section 14.1, however, with the exception of severe combined immunodeficiency, benefit from vaccination is likely to outweigh the risk in other types of immunosuppression—if there is any doubt, seek specialist advice; also predisposition to, or history of, intussusception

Side-effects see section 14.1

Indications and dose

Immunisation against gastro-enteritis caused by rotavirus

- By mouth

Child over 6 weeks 2 doses of 1.5 mL, separated by an interval of at least 4 weeks; first dose must be given between 6–15 weeks of age; course should be completed before 24 weeks of age (preferably before 16 weeks)

Rotarix® (GSK) (PoM)

Oral suspension, live attenuated rotavirus (RIX4414 strain), net price 1.5 mL prefilled oral syringe = £34.76

Rubella vaccine

A combined measles, mumps and rubella vaccine (MMR vaccine) aims to eliminate rubella (German measles) and congenital rubella syndrome. MMR vaccine is used for childhood vaccination as well as for vaccinating adults (including women of child-bearing age) who do not have immunity against rubella the combined live measles, mumps and rubella vaccine is a suitable alternative.

Single antigen vaccine

No longer available in the UK; see MMR vaccine, p. 618

Combined vaccines

see MMR vaccine

Smallpox vaccine

Limited supplies of **smallpox vaccine** are held at the Specialist and Reference Microbiology Division, Public Health England Colindale (Tel. (020) 8200 4400) for the exclusive use of workers in laboratories where pox viruses (such as vaccinia) are handled.

If a wider use of the vaccine is being considered, *Guidelines for smallpox response and management in the post-eradication era* should be consulted at www.hpa.org.uk.

Tetanus vaccines

Tetanus vaccine contains a cell-free purified toxin of *Clostridium tetani* adsorbed on aluminium hydroxide or aluminium phosphate to improve antigenicity.

Primary immunisation for children under 10 years consists of 3 doses of a combined preparation containing adsorbed tetanus vaccine (see Diphtheria-containing Vaccines), with an interval of 1 month between doses. Following routine childhood vaccination, 2 booster doses of a preparation containing adsorbed tetanus vaccine are recommended, the first before school entry and the second before leaving school. (see Immunisation schedule, section 14.1).

The recommended schedule of tetanus vaccination not only gives protection against tetanus in childhood but also gives the basic immunity for subsequent booster doses. In most circumstances, a total number of 5 doses of tetanus vaccine is considered sufficient for long-term protection.

For primary immunisation of children over 10 years previously unimmunised against tetanus, 3 doses of **adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine** are given with an interval of 1 month between doses (see Diphtheria-containing Vaccines).

Cautions See also Section 14.1. When a child presents for a booster dose but has been vaccinated following a tetanus-prone wound, the vaccine preparation administered at the time of injury should be determined. If this is not possible, the booster should still be given to ensure adequate protection against all antigens in the booster vaccine.

Very rarely, tetanus has developed after abdominal surgery; carers of children awaiting elective surgery should be asked about the child's tetanus immunisation status and the child should be immunised if necessary.

Parenteral drug abuse is also associated with tetanus; those abusing drugs by injection should be vaccinated if unimmunised—booster doses should be given if there is any doubt about their immunisation status.

Travel recommendations see section 14.6.

Contra-indications See section 14.1

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects See section 14.1

Wounds Wounds are considered to be tetanus-prone if they are sustained more than 6 hours before surgical treatment or at any interval after injury and are puncture-type (particularly if contaminated with soil or manure) or show much devitalised tissue or are septic or are compound fractures or contain foreign bodies. All wounds should receive thorough cleansing.

- For **clean wounds**: fully immunised individuals (those who have received a total of 5 doses of a tetanus-containing vaccine at appropriate intervals) and those whose primary immunisation is complete (with boosters up to date), do not require tetanus vaccine; individuals whose primary immunisation is incomplete or whose boosters are not up to date require a reinforcing dose of a tetanus-containing vaccine (followed by further doses as required to complete the schedule); non-immunised individuals (or those whose immunisation status is not known or who have been fully immunised but are now immunocompromised) should be given a dose of the appropriate tetanus-containing vaccine immediately (followed by completion of the full course of the vaccine if records confirm the need).
- For **tetanus-prone wounds**: management is as for clean wounds with the addition of a dose of tetanus immunoglobulin (section 14.5.2) given at a different site; in fully immunised individuals and those whose primary immunisation is complete (with boosters up to date) the immunoglobulin is needed only if the risk of infection is especially high (e.g. contamination with manure). Antibacterial prophylaxis (with benzylpenicillin, co-amoxiclav, or metronidazole) may also be required for tetanus-prone wounds.

Combined vaccines

See Diphtheria-containing Vaccines

Tick-borne encephalitis vaccine

Tick-borne encephalitis vaccine contains inactivated tick-borne encephalitis virus cultivated in chick embryo cells. It is recommended for immunisation of those living in or visiting high-risk areas (see International Travel, section 14.6). Children walking or camping in warm forested areas of Central and Eastern Europe, Scandinavia, Northern and Eastern China, and some parts of Japan, particularly from April to November when ticks are most prevalent, are at greatest risk of tick-borne encephalitis. For full protection, 3 doses of the vaccine are required; booster doses are required every 3–5 years for those still at risk. Ideally, immunisation should be completed at least one month before travel.

TICK-BORNE ENCEPHALITIS VACCINE, INACTIVATED

Cautions see section 14.1

Contra-indications see section 14.1

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects see section 14.1

Indications and dose

Immunisation against tick-borne encephalitis

- By intramuscular injection in deltoid region or anterolateral thigh in infants

Child 1–16 years initial immunisation, 3 doses of 0.25 mL, second dose after 1–3 months and third dose after a further 5–12 months

Child 16–18 years 3 doses each of 0.5 mL, second dose after 1–3 months and third dose after further 5–12 months

Immunocompromised (including those receiving immunosuppressants), antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved

Note To achieve more rapid protection, second dose may be given 14 days after first dose.

Booster doses, give first dose within 3 years after initial course, then every 3–5 years

TicoVac® (MASTA) (PoM)

Injection, suspension, formaldehyde-inactivated Neudörfl tick-borne encephalitis virus strain, (cultivated in chick embryo cells) adsorbed onto hydrated aluminium hydroxide, net price 0.25-mL prefilled syringe (*TicoVac Junior*®) = £28.00, 0.5-mL prefilled syringe = £32.00

Excipients include gentamicin and neomycin

Typhoid vaccines

Typhoid vaccine is available as Vi capsular polysaccharide (from *Salmonella typhi*) vaccine for injection and as live attenuated *Salmonella typhi* vaccine for oral use.

Typhoid immunisation is advised for children travelling to:

- areas where typhoid is endemic, especially if staying with or visiting local people;
- endemic areas where frequent or prolonged exposure to poor sanitation and poor food hygiene is likely.

Typhoid vaccination is not a substitute for scrupulous personal hygiene (see p. 632).

Capsular polysaccharide typhoid vaccine is usually given by intramuscular injection. Children under 2 years may respond suboptimally to the vaccine, but children aged between 1–2 years should be immunised if the risk of typhoid fever is considered high (immunisation is not recommended for infants under 12 months). Revaccination is needed every 3 years on continued exposure.

Oral typhoid vaccine is a live attenuated vaccine contained in an enteric-coated capsule. One capsule taken on alternate days for a total of 3 doses provides protection 7–10 days after the last dose. Protection may persist for up to 3 years in those constantly (or repeatedly) exposed to *Salmonella typhi*, but those who only occasionally travel to endemic areas require further courses at intervals of 1 year.

Interactions Oral typhoid vaccine is inactivated by concomitant administration of antibacterials or antimalarials:

- Antibacterials should be avoided for 3 days before and after oral typhoid vaccination;
- Mefloquine should be avoided for at least 12 hours before or after oral typhoid;
- For other antimalarials, vaccination with oral typhoid vaccine should be completed at least 3 days before the first dose of the antimalarial (except proguanil hydrochloride with atovaquone, which may be given concomitantly).

TYPHOID VACCINE

Cautions section 14.1; **interactions**: see above and Appendix 1 (vaccines)

Contra-indications section 14.1; also for oral vaccine, acute gastro-intestinal illness

Pregnancy see p. 605

Breast-feeding see p. 605

Side-effects section 14.1

Indications and dose

Immunisation against typhoid fever

For dose see under preparations

▲Typhoid polysaccharide vaccine for injection

Typherix® (GSK) (PoM)

Injection, Vi capsular polysaccharide typhoid vaccine, 50 micrograms/mL virulence polysaccharide antigen of *Salmonella typhi*, net price 0.5-mL prefilled syringe = £9.93

Note May be difficult to obtain

Dose

- By intramuscular injection
 - **Child under 2 years** [unlicensed use], 0.5 mL, at least 2 weeks before potential exposure to typhoid infection; response may be suboptimal (see notes above)
 - **Child 2–18 years** 0.5 mL, at least 2 weeks before potential exposure to typhoid infection

Typhim Vi® (Sanofi Pasteur) (PoM)

Injection, Vi capsular polysaccharide typhoid vaccine, 50 micrograms/mL virulence polysaccharide antigen of formaldehyde-inactivated *Salmonella typhi*, net price 0.5-mL prefilled syringe = £9.30

Dose

- By intramuscular injection
 - **Child under 2 years** [unlicensed use], 0.5 mL, at least 2 weeks before potential exposure to typhoid infection; response may be suboptimal (see notes above)
 - **Child 2–18 years** 0.5 mL, at least 2 weeks before potential exposure to typhoid infection

▲Polysaccharide vaccine with hepatitis A vaccine

See Hepatitis A Vaccine

▲Typhoid vaccine, live (oral)

Vivotif® (Crucell) (PoM)

Capsules, e/c, live attenuated *Salmonella typhi* (Ty21a), net price 3-cap pack = £14.77. Label: 25, counselling, administration

Dose

- By mouth
 - **Child 6–18 years** 1 capsule on days 1, 3, and 5
 - **Counselling** Take one hour before a meal. Swallow as soon as possible after placing in mouth with a cold or lukewarm drink; it is important to store capsules in a refrigerator

Varicella–zoster vaccine

Varicella–zoster vaccine (live) is licensed for immunisation against varicella (chickenpox) in seronegative individuals. It is not recommended for routine use in children but can be given to seronegative healthy children over 1 year who come into close contact with individuals at high risk of severe varicella infections.

Rarely, the varicella–zoster vaccine virus has been transmitted from the vaccinated individual to close contacts. Therefore, contact with the following should be avoided if a vaccine-related cutaneous rash develops within 4–6 weeks of the first or second dose:

- varicella-susceptible pregnant females;
- individuals at high risk of severe varicella, including those with immunodeficiency or those receiving immunosuppressive therapy.

Varicella–zoster immunoglobulin is used to protect susceptible children at increased risk of varicella infection, see p. 631.

VARICELLA–ZOSTER VACCINE

Cautions see section 14.1; also post-vaccination close-contact with susceptible individuals (see notes above)

Contra-indications see section 14.1

Pregnancy avoid pregnancy for 3 months after vaccination; see also p. 605

Breast-feeding see p. 605

Side-effects see section 14.1; also conjunctivitis and varicella-like rash; *rarely* thrombocytopenia

Indications and dose

Immunisation against varicella (chickenpox) infection (see notes above)

For dose, see under preparations

Varilrix® (GSK) (PoM)

Injection, powder for reconstitution, live attenuated varicella–zoster virus (Oka strain) propagated in human diploid cells, net price 0.5-mL vial (with diluent) = £27.31

Excipients include neomycin

Dose

- By subcutaneous injection preferably into deltoid region

Child 1–18 years (see notes above), 2 doses of 0.5 mL separated by an interval of at least 6 weeks (minimum 4 weeks)

Varivax® (Sanofi Pasteur) (PoM)

Injection powder for reconstitution, live attenuated varicella–zoster virus (Oka/Merck strain) propagated in human diploid cells, net price 0.5-mL vial (with diluent) = £30.28

Excipients include gelatin and neomycin

Dose

- By intramuscular or subcutaneous injection into deltoid region (or higher anterolateral thigh in young children)

Child 1–13 years (see notes above) 2 doses of 0.5 mL separated by an interval of at least 4 weeks (2 doses separated by 12 weeks in children with asymptomatic HIV infection)

Child 13–18 years 2 doses of 0.5 mL separated by 4–8 weeks

Yellow fever vaccine

Live yellow fever vaccine is indicated for those travelling to or living in areas where infection is endemic (see

p. 632). Infants under 6 months of age should not be vaccinated because there is a small risk of encephalitis; infants aged 6–9 months should be vaccinated only if the risk of yellow fever is high and unavoidable (seek expert advice). The immunity which probably lasts for life is officially accepted for 10 years starting from 10 days after primary immunisation and for a further 10 years immediately after revaccination.

Very rarely vaccine-associated adverse effects have been reported, such as viscerotropic disease (yellow fever vaccine-associated viscerotropic disease, YEL-AVD), a syndrome which may include metabolic acidosis, muscle and liver cytolysis, and multi-organ failure. Neurological disorders (yellow fever vaccine-associated neurotropic disease, YEL-AND) such as encephalitis have also been reported. These *very rare* adverse effects have usually occurred after the first dose of yellow fever vaccine in those with no previous immunity.

Pregnancy Live yellow fever vaccine should not be given during pregnancy because there is a theoretical risk of fetal infection. Pregnant women should be advised not to travel to areas at high risk of yellow fever. If exposure cannot be avoided during pregnancy, then the vaccine should be given if the risk from disease in the mother outweighs the risk to the fetus from vaccination.

Breast-feeding Avoid; seek specialist advice if exposure to virus cannot be avoided.

YELLOW FEVER VACCINE, LIVE

Cautions see section 14.1

Contra-indications see section 14.1 and notes above; also children under 6 months; history of thymus dysfunction

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see section 14.1; also reported neurotropic disease, and viscerotropic disease (see notes above)

Indications and dose

Immunisation against yellow fever

- By deep subcutaneous injection

Child 9 months–18 years 0.5 mL (see also notes above)

Yellow Fever Vaccine, Live (PoM)

Yel(live)

Injection, powder for reconstitution, live, attenuated 17D-204 strain of yellow fever virus, cultivated in chick embryos; single dose vial with syringe containing 0.5 mL diluent

Available (only to designated Yellow Fever Vaccination centres) as *Stamari®*

14.5 Immunoglobulins

14.5.1 Normal Immunoglobulin

14.5.2 Disease-specific immunoglobulins

14.5.3 Anti-D (Rh₀) immunoglobulin

Two types of human immunoglobulin preparation are available, **normal immunoglobulin** and **disease-specific immunoglobulins**.

Human immunoglobulin is a sterile preparation of concentrated antibodies (immune globulins) recovered from pooled human plasma or serum obtained from outside the UK, tested and found non-reactive for hepatitis B surface antigen and for antibodies against hepatitis C virus and human immunodeficiency virus (types 1 and 2). A global shortage of human immunoglobulin and the rapidly increasing range of clinical indications for treatment with immunoglobulins has resulted in the need for a Demand Management programme in the UK (for further information consult www.ivig.nhs.uk and *Clinical Guidelines for Immunoglobulin Use*, www.gov.uk/dh).

Immunoglobulins of animal origin (antisera) were frequently associated with hypersensitivity reactions and are no longer used.

Further information on the use of immunoglobulins is included in the Health Protection Agency's *Immunoglobulin Handbook*: www.hpa.org.uk and in the Department of Health's publication, *Immunisation against Infectious Disease*, www.gov.uk/dh.

Availability Normal immunoglobulin for intramuscular administration is available from some regional Public Health laboratories for protection of contacts and the control of outbreaks of hepatitis A, measles, and rubella only. For other indications, subcutaneous or intravenous normal immunoglobulin should be purchased from the manufacturer.

Disease-specific immunoglobulins (section 14.5.2) are available from some regional Public Health laboratories with the exception of **tetanus immunoglobulin** which is available from BPL, hospital pharmacies, or blood transfusion departments. **Rabies immunoglobulin** is available from the Specialist and Reference Microbiology Division, Public Health England, Colindale. **Hepatitis B immunoglobulin** required by transplant centres should be obtained commercially.

In Scotland all immunoglobulins are available from the *Scottish National Blood Transfusion Service* (SNBTS).

In Wales all immunoglobulins are available from the *Welsh Blood Service* (WBS).

In Northern Ireland all immunoglobulins are available from the *Northern Ireland Blood Transfusion Service* (NI BTS).

14.5.1 Normal Immunoglobulin

Human **normal immunoglobulin** ('HNIG') is prepared from pools of at least 1000 donations of human plasma; it contains immunoglobulin G (IgG) and antibodies to hepatitis A, measles, mumps, rubella, varicella, and other viruses that are currently prevalent in the general population.

Normal immunoglobulin may **interfere with the immune response to live virus vaccines** which should therefore only be given **at least 3 weeks before or 3 months after** an injection of normal immunoglobulin (this does not apply to yellow fever vaccine since normal immunoglobulin does not contain antibody to this virus).

Uses Normal immunoglobulin (containing 10–18% protein) is administered by **intramuscular injection** for the protection of susceptible contacts against **hepatitis A virus** (infectious hepatitis), **measles** and, to a lesser extent, **rubella**. Injection of immunoglobulin produces immediate protection lasting for several weeks.

Normal immunoglobulin (containing 3–12% protein) for *intravenous administration* is used as **replacement therapy** for children with congenital agammaglobulinaemia and hypogammaglobulinaemia, and for the short-term treatment of idiopathic thrombocytopenic purpura and Kawasaki disease; it is also used for the prophylaxis of infection following bone-marrow transplantation and in children with symptomatic HIV infection who have recurrent bacterial infections. Normal immunoglobulin for replacement therapy may also be given intramuscularly or subcutaneously, but intravenous formulations are normally preferred. Intravenous immunoglobulin is also used in the treatment of Guillain-Barré syndrome as an alternative to plasma exchange.

The dose of normal immunoglobulin used as replacement therapy in patients with immunodeficiencies is **not the same** as the dose required for treatment of acute conditions. For Kawasaki disease a single dose of 2 g/kg by intravenous infusion should be given with concomitant aspirin (see section 2.9) within 10 days of onset of symptoms (but children with a delayed diagnosis may also benefit).

For guidance on the use of intravenous normal immunoglobulins and alternative therapies for other conditions, consult *Clinical Guidelines for Immunoglobulin Use* (www.gov.uk/dh).

Hepatitis A **Hepatitis A vaccine** is preferred for children at risk of infection (see p. 612) including those visiting areas where the disease is highly endemic (all countries excluding Northern and Western Europe, North America, Japan, Australia, and New Zealand). In unimmunised children, transmission of hepatitis A is reduced by good hygiene. Intramuscular normal immunoglobulin is no longer recommended for routine prophylaxis in travellers, but it may be indicated for immunocompromised patients if their antibody response to the vaccine is unlikely to be adequate.

Intramuscular normal immunoglobulin is recommended for prevention of infection in close contacts (of confirmed cases of hepatitis A) who have chronic liver disease or HIV infection, or who are immunosuppressed; normal immunoglobulin should be given as soon as possible, preferably within 14 days of exposure to the primary case. However, normal immunoglobulin can still be given to contacts at risk of severe disease up to 28 days after exposure to the primary case. Hepatitis A vaccine can be given at the same time, but it should be given at a separate injection site.

Measles Intravenous or subcutaneous normal immunoglobulin may be given to prevent or attenuate an attack of measles in children with compromised immunity. Children with compromised immunity who have come into contact with measles should receive intravenous or subcutaneous normal immunoglobulin as soon as possible after exposure. It is most effective if given within 72 hours but can be effective if given within 6 days.

Subcutaneous or intramuscular normal immunoglobulin should also be considered for the following individuals if they have been in contact with a confirmed case of measles or with a person associated with a local outbreak:

- non-immune pregnant women
- infants under 9 months

Further advice should be sought from the Centre for Infections, Public Health England (tel. (020) 8200 6868).

Children with normal immunity who are not in the above categories and who have not been fully immunised against measles, can be given MMR vaccine (section 14.4) for prophylaxis following exposure to measles.

Rubella Intramuscular immunoglobulin after exposure to rubella does **not** prevent infection in non-immune contacts and is **not** recommended for protection of pregnant females exposed to rubella. It may, however, reduce the likelihood of a clinical attack which may possibly reduce the risk to the fetus. Risk of intrauterine transmission is greatest in the first 11 weeks of pregnancy, between 16 and 20 weeks there is a minimal risk of deafness only, after 20 weeks there is no increased risk. Intramuscular normal immunoglobulin should be used only if termination of pregnancy would be unacceptable to the pregnant individual—it should be given as soon as possible after exposure. Serological follow-up of recipients is essential.

For routine prophylaxis, see MMR vaccine (p. 618).

NORMAL IMMUNOGLOBULIN

Cautions hypo- or agammaglobulinaemia with or without IgA deficiency; interference with live virus vaccines—see p. 628

Intravenous use Thrombophilic disorders, or risk factors for arterial or venous thromboembolic events; obesity; ensure adequate hydration, renal insufficiency

Contra-indications patients with selective IgA deficiency who have known antibody against IgA

Renal impairment monitor for acute renal failure; consider discontinuation if renal function deteriorates. Intravenous preparations with added sucrose have been associated with cases of renal dysfunction and acute renal failure

Side-effects nausea, diarrhoea, chills, fever, headache, dizziness, arthralgia, myalgia, muscle spasms, low back pain; *rarely* hypotension, anaphylaxis, cutaneous skin reactions, aseptic meningitis, acute renal failure; also reported with *intravenous use*, injection site reactions, abdominal pain and distension, blood pressure fluctuations, haemolytic anaemia, thromboembolic events including myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis

Note Adverse reactions are more likely to occur in patients receiving normal immunoglobulin for the first time, or following a prolonged period between treatments, or when a different brand of normal immunoglobulin is administered.

Indications and dose

See under preparations

Note Antibody titres can vary widely between normal immunoglobulin preparations from different manufacturers—formulations are **not interchangeable**; patients should be maintained on the same formulation throughout long-term treatment to avoid adverse effects

For intramuscular use

Normal Immunoglobulin (PoM)

Normal immunoglobulin injection. 250-mg vial; 750-mg vial
Dose

To control outbreaks of hepatitis A (see notes above)

- By deep intramuscular injection
 - Child under 10 years 250 mg
 - Child 10–18 years 500 mg

Rubella in pregnancy, prevention of clinical attack

- By deep intramuscular injection
 - 750 mg

Available from the Centre for Infections and other regional Health Protection Agency offices (for contacts and control of outbreaks only, see above)

For subcutaneous use

Note Preparations for subcutaneous use may be administered by intramuscular injection if subcutaneous route not possible; intramuscular route not recommended for patients with thrombocytopenia or other bleeding disorders

Gammanorm® (Octapharma) (PoM)

Normal immunoglobulin (protein 16.5%) injection, net price 1.65 g (10 mL) = £96.77, 3.3 g (20 mL) = £193.55

Electrolytes Na⁺ 1.09 mmol/10-mL vial

Dose

Antibody deficiency syndromes

- By subcutaneous infusion
 - Consult product literature

Hizentra® (CSL Behring) ▼ (PoM)

Normal immunoglobulin (protein 20%) injection, net price 1 g (5 mL) = £45.90, 2 g (10 mL) = £91.80, 4 g (20 mL) = £183.60

Note Contains L-proline; contra-indicated in patients with hyperprolinaemia

Dose

Antibody deficiency syndromes

- By subcutaneous infusion
 - Consult product literature

Subcuvia® (Baxter) (PoM)

Normal immunoglobulin (protein 16%) injection, net price 800 mg (5 mL) = £32.56, 1.6 g (10 mL) = £65.12

Dose

Antibody deficiency syndromes

- By subcutaneous infusion
 - Consult product literature (not licensed for use in children under 12 years)

Subgam® (BPL) (PoM)

Normal immunoglobulin (protein 14–18%) injection, net price 250-mg vial = £11.20, 750-mg vial = £34.20, 1.5-g vial = £68.40

Dose

Antibody deficiency syndromes

- By subcutaneous infusion
 - Consult product literature

Hepatitis A prophylaxis (see also notes above)

- By intramuscular injection
 - Child under 10 years 500 mg
 - Child 10–18 years 750 mg

Rubella prophylaxis in pregnancy (see also notes above)

- By intramuscular injection
 - 750 mg

Note Subgam® is not licensed for prophylactic use, but due to difficulty in obtaining suitable immunoglobulin products, the Health Protection Agency recommends intramuscular use for prophylaxis against Hepatitis A, or rubella

For intravenous use

Note Dose recommendation for Kawasaki disease, see section 14.5.1; other indications—consult product literature for dosage regimens

Aragam® (Oxbridge) (PoM)

Intravenous infusion, human normal immunoglobulin (protein 5%), net price 2.5 g (50 mL) = £145.00, 5 g (100 mL) = £290.00, 10 g (200 mL) = £580.00, 20 g (400 mL) = £1160.00

Excipients include glucose 50 mg/mL

Flebogamma® DIF (Grifols) (PoM)

Intravenous infusion, human normal immunoglobulin, protein 5%, net price 0.5 g (10 mL) = £30.00, 2.5 g (50 mL) = £150.00, 5 g (100 mL) = £300.00, 10 g (200 mL) = £600.00, 20 g (400 mL) = £1200.00; protein 10%, 5 g (50 mL) = £300.00, 10 g (100 mL) = £600.00, 20 g (200 mL) = £1200.00

Note Both strengths contain sorbitol 50 mg/mL; contra-indicated in patients with hereditary fructose intolerance

Gammagard S/D® (Baxter) (PoM)

Intravenous infusion, powder for reconstitution, human normal immunoglobulin (providing protein 5% or 10%), net price 5 g (with diluent) = £200.50, 10 g (with diluent) = £401.00

Gammaplex® (BPL) (PoM)

Intravenous infusion, human normal immunoglobulin (protein 5%), net price 2.5 g (50 mL) = £104.50, 5 g (100 mL) = £209.00, 10 g (200 mL) = £418.00

Note Contains sorbitol 50 mg/mL; contra-indicated in patients with hereditary fructose intolerance

Gamunex® (Grifols) (PoM)

Intravenous infusion, human normal immunoglobulin (protein 10%), net price 5 g (50 mL) = £250.00, 10 g (100 mL) = £500.00, 20 g (200 mL) = £1000.00

Note Use Glucose 5% intravenous infusion if dilution prior to infusion required

Intratect® (Biotest UK) (PoM)

Intravenous infusion, human normal immunoglobulin, protein 5%, net price 1 g (20 mL) = £45.00, 2.5 g (50 mL) = £112.50, 5 g (100 mL) = £225.00, 10 g (200 mL) = £450.00; protein 10%, 1 g (10 mL) = £45.00, 5 g (50 mL) = £225.00, 10 g (100 mL) = £450.00, 20 g (200 mL) = £900.00

Kiovig® (Baxter) (PoM)

Intravenous infusion, human normal immunoglobulin (protein 10%), net price 1 g (10 mL) = £49.00, 2.5 g (25 mL) = £122.50, 5 g (50 mL) = £245.00, 10 g (100 mL) = £490.00, 20 g (200 mL) = £980.00, 30 g (300 mL) = £1470.00

Note Use Glucose 5% intravenous infusion, if dilution prior to administration is required

Octagam® (Octapharma) (PoM)

Intravenous infusion, human normal immunoglobulin, protein 5%, net price 2.5 g (50 mL) = £1.02, 5 g (100 mL) = £2.04, 10 g (200 mL) = £2.04; protein 10%, 2 g (20 mL) = £117.30, 5 g (50 mL) = £293.25, 10 g (100 mL) = £586.50, 20 g (200 mL) = £1173.00

Note Contains maltose (may cause falsely elevated results with blood glucose testing systems)

Privigen® (CSL Behring) (PoM)

Intravenous infusion, human normal immunoglobulin (protein 10%), net price 2.5 g (25 mL) = £114.75, 5 g (50 mL) = £229.50, 10 g (100 mL) = £459.00, 20 g (200 mL) = £918.00

Note Contains L-proline; contra-indicated in patients with hyperprolinaemia

Vigam® (BPL) (PoM)

Intravenous infusion, human normal immunoglobulin (protein 5%), net price 2.5 g (50 mL) = £95.00, 5 g (100 mL) = £209.00, 10 g (200 mL) = £418.00

Note Contains sucrose (see Renal Impairment above)

14.5.2 Disease-specific immunoglobulins

Specific immunoglobulins are prepared by pooling the plasma of selected human donors with high levels of the specific antibody required. For further information, see *Immunoglobulin Handbook* (www.hpa.org.uk).

There are no specific immunoglobulins for hepatitis A, measles, or rubella—normal immunoglobulin, section 14.5.1 is used in certain circumstances. There is no specific immunoglobulin for mumps; neither normal immunoglobulin nor MMR vaccine is effective as post-exposure prophylaxis.

Hepatitis B

Disease-specific **hepatitis B immunoglobulin** ('HBIG') is available for use in association with hepatitis B vaccine for the prevention of infection in infants born to mothers who have become infected with this virus in pregnancy or who are high-risk carriers (see Hepatitis B Vaccine, p. 614). Hepatitis B immunoglobulin will not inhibit the antibody response when given at the same time as hepatitis B vaccine, but should be given at different sites.

An intravenous preparation of hepatitis B-specific immunoglobulin is licensed for the prevention of hepatitis B recurrence in HBV-DNA negative patients who have undergone liver transplantation for liver failure caused by the virus.

HEPATITIS B IMMUNOGLOBULIN

Cautions IgA deficiency; interference with live virus vaccines—see under Normal Immunoglobulin, p. 628

Side-effects injection site swelling and pain, arthralgia; rarely anaphylaxis chest tightness, dyspnoea; also reported tremor, dizziness, facial oedema, glossitis, and buccal ulceration; for side-effects associated with intravenous immunoglobulins, see section 14.5.1

Indications and dose

See under preparations and see also notes above

Hepatitis B Immunoglobulin (PoM)

Injection, hepatitis B-specific immunoglobulin, 100 units/mL. Vials containing 200 units or 500 units, available from selected Health Protection Agency and NHS laboratories (except for Transplant Centres, see p. 628), also available from BPL

Dose**Prophylaxis against hepatitis B infection**

- By intramuscular injection
(as soon as possible after exposure; ideally within 48 hours, but no later than 7 days after exposure)

Child 1 month–5 years 200 units

Child 5–10 years 300 units

Child 10–18 years 500 units

Prevention of transmitted infection at birth

- By intramuscular injection

Neonate 200 units as soon as possible after birth; for full details consult *Immunisation against Infectious Disease* (www.dh.gov.uk)

Hepatect® CP (Biotest UK) (PoM)

Intravenous infusion, hepatitis B-specific immunoglobulin 50 units/mL, net price 500 units (10 mL) = £300.00, 2000 units (40 mL) = £1100.00, 5000 units (100 mL) = £3000.00

Dose

Following exposure to hepatitis B virus-contaminated material (as soon as possible after exposure, but no later than 72 hours); prevention of transmitted infection at birth; prophylaxis against re-infection of transplanted liver

Consult product literature

Rabies

Following exposure of an unimmunised child to an animal in or from a country where the risk of rabies is high, the site of the bite should be washed with soapy water and specific **rabies immunoglobulin** of human origin should be administered. All of the dose should be injected around the site of the wound; if this is difficult or the wound has completely healed it can be given in the anterolateral thigh (remote from the site used for vaccination). Rabies vaccine should also be given intramuscularly at a different site (for details see Rabies Vaccine, p. 623). If there is delay in giving the rabies immunoglobulin, it should be given within 7 days of starting the course of rabies vaccine.

RABIES IMMUNOGLOBULIN

Cautions IgA deficiency; interference with live virus vaccines—see p. 628 under Normal Immunoglobulin

Side-effects injection site swelling and pain; *rarely* anaphylaxis; buccal ulceration, glossitis, chest tightness, dyspnoea, tremor, dizziness, arthralgia, and facial oedema also reported

Indications and dose**Post-exposure prophylaxis against rabies infection**

- **By intramuscular injection**

20 units/kg, *by infiltration* in and around the cleansed wound; if the wound not visible or healed or if infiltration of whole volume not possible, give remainder *by intramuscular injection* into anterolateral thigh (remote from vaccination site)

Note The potency of individual batches of rabies immunoglobulin from the manufacturer may vary; potency may also be described differently by different manufacturers. It is therefore critical to know the potency of the batch to be used and the weight of the patient in order to calculate the specific volume required to provide the necessary dose

Rabies Immunoglobulin (PoM)

(Antirabies Immunoglobulin Injection)

See notes above

Available from Specialist and Reference Microbiology Division, Public Health England (see section 14.5 under Availability) (also from BPL)

Tetanus

Tetanus immunoglobulin, together with metronidazole (section 5.1.11) and wound cleansing, should also be used for the treatment of established cases of tetanus.

For the management of tetanus-prone wounds, **tetanus immunoglobulin** of human origin should be used in addition to wound cleansing and, where appropriate, antibacterial prophylaxis and a tetanus-containing vaccine (see Diphtheria-containing Vaccines, section 14.4).

TETANUS IMMUNOGLOBULIN

Cautions IgA deficiency; interference with live virus vaccines—see, p. 628

Side-effects injection site swelling and pain; *rarely* anaphylaxis; buccal ulceration; glossitis, chest tightness, dyspnoea, tremor, dizziness, arthralgia, and facial oedema also reported

Indications and dose**Post-exposure prophylaxis**

- **By intramuscular injection**

250 units, increased to 500 units if more than 24 hours have elapsed or there is risk of heavy contamination or following burns

Treatment of tetanus infection

- **By intramuscular injection**

150 units/kg (multiple sites)

Tetanus Immunoglobulin (PoM)

(Antitetanus Immunoglobulin Injection)

Available from BPL

Note May be difficult to obtain

Varicella–zoster

Varicella–zoster immunoglobulin (VZIG) is recommended for individuals who are at increased risk of severe varicella *and* who have no antibodies to varicella–zoster virus *and* who have significant exposure to chickenpox or herpes zoster. Those at increased risk include:

- neonates whose mothers develop chickenpox in the period 7 days before to 7 days after delivery;
- susceptible neonates exposed in the first 7 days of life;
- susceptible neonates or infants exposed whilst requiring intensive or prolonged special care nursing;
- susceptible women exposed at any stage of pregnancy (but when supplies of VZIG are short, may only be issued to those exposed in the first 20 weeks' gestation or to those near term) providing VZIG is given within 10 days of contact;
- immunocompromised individuals including those who have received corticosteroids in the previous 3 months at the following dose equivalents of prednisolone: *children* 2 mg/kg daily (or more than 40 mg) for at least 1 week or 1 mg/kg daily for 1 month.

Important: for full details consult *Immunisation against Infectious Disease*. **Varicella–zoster vaccine** is available—see section 14.4.

For treatment of varicella–zoster infections and attenuation of infection if varicella–zoster immunoglobulin not indicated, see section 5.3.2.1

VARICELLA–ZOSTER IMMUNOGLOBULIN

Cautions IgA deficiency; interference with live virus vaccines—see p. 628 under Normal Immunoglobulins

Side-effects injection site swelling and pain; *rarely* anaphylaxis

Indications and dose**Prophylaxis against varicella infection (as soon as possible—not later than 10 days after exposure)**

● By deep intramuscular injection

Neonate 250 mg**Child 1 month–6 years** 250 mg**Child 6–11 years** 500 mg**Child 11–15 years** 750 mg**Child 15–18 years** 1 g

Give second dose if further exposure occurs more than 3 weeks after first dose

Note No evidence that effective in treatment of severe disease.

Normal immunoglobulin for intravenous use (section 14.5.1) may be used in those unable to receive intramuscular injection.

Varicella–Zoster Immunoglobulin [PoM]
(Antivaricella–zoster Immunoglobulin)

Available from selected Health Protection Agency and NHS laboratories (see section 14.5 under Availability) (also from BPL)

**14.5.3 Anti-D (Rh)
immunoglobulin**This section is not included in *BNF for Children*. See BNF for use of Anti-D (Rh)₀ immunoglobulin**14.6 International travel****Note** For advice on **malaria chemoprophylaxis**, see section 5.4.1.

No special immunisation is required for travellers to the United States, Europe, Australia, or New Zealand although all travellers should have immunity to tetanus and poliomyelitis (and childhood immunisations should be up to date); see also Tick-borne Encephalitis, p. 625. Certain precautions are required in Non-European areas surrounding the Mediterranean, in Africa, the Middle East, Asia, and South America.

Travellers to areas that have a high incidence of **poliomyelitis** or **tuberculosis** should be immunised with the appropriate vaccine; in the case of poliomyelitis previously immunised adults may be given a booster dose of a preparation containing inactivated poliomyelitis vaccine. BCG immunisation is recommended for travellers aged under 16 years proposing to stay for longer than 3 months (or in close contact with the local population) in countries with an incidence¹ of tuberculosis greater than 40 per 100 000; it should preferably be given three months or more before departure.

Yellow fever immunisation is recommended for travel to the endemic zones of Africa and South America. Many countries require an International Certificate of Vaccination from individuals arriving from, or who have been travelling through, endemic areas, whilst other countries require a certificate from all entering travellers (consult the Department of Health handbook, *Health Information for Overseas Travel*, www.dh.gov.uk).

1. List of countries where the incidence of tuberculosis is greater than 40 cases per 100 000 is available at www.hpa.org.uk

Immunisation against **meningococcal meningitis** is recommended for a number of areas of the world (for details, see p. 619).

Protection against **hepatitis A** is recommended for travellers to high-risk areas outside Northern and Western Europe, North America, Japan, Australia and New Zealand. Hepatitis A vaccine (see p. 612) is preferred and it is likely to be effective even if given shortly before departure; normal immunoglobulin is no longer given routinely but may be indicated in the immunocompromised (see p. 628). Special care must also be taken with food hygiene (see below).

Hepatitis B vaccine (see p. 614) is recommended for those travelling to areas of high prevalence who plan to remain there for lengthy periods and who may therefore be at increased risk of acquiring infection as the result of medical or dental procedures carried out in those countries. Short-term tourists are not generally at increased risk of infection but may place themselves at risk by their sexual behaviour when abroad.

Prophylactic immunisation against **rabies** (see p. 623) is recommended for travellers to enzootic areas on long journeys or to areas out of reach of immediate medical attention.

Travellers who have not had a **tetanus** booster in the last 10 years and are visiting areas where medical attention may not be accessible should receive a booster dose of adsorbed diphtheria [low dose], tetanus and inactivated poliomyelitis vaccine (see p. 609), even if they have received 5 doses of a tetanus-containing vaccine previously.

Typhoid vaccine is indicated for travellers to countries where typhoid is endemic, but the vaccine is no substitute for personal precautions (see below).

There is no requirement for cholera vaccination as a condition for entry into any country, but **oral cholera vaccine** (see p. 609) should be considered for backpackers and those travelling to situations where the risk is greatest (e.g. refugee camps). Regardless of vaccination, travellers to areas where cholera is endemic should take special care with food hygiene (see below).

Advice on **diphtheria** (see p. 609), on **Japanese encephalitis** (see p. 618), and on **tick-borne encephalitis** (see p. 625) is included in *Health Information for Overseas Travel*, see below.

Food hygiene In areas where sanitation is poor, good food hygiene is important to help prevent hepatitis A, typhoid, cholera, and other diarrhoeal diseases (including travellers' diarrhoea). Food should be freshly prepared and hot, and uncooked vegetables (including green salads) should be avoided; only fruits which can be peeled should be eaten. Only suitable bottled water, or tap water that has been boiled, or treated with sterilising tablets should be used for drinking.

Information on health advice for travellers

Health professionals and travellers can find the latest information on immunisation requirements and precautions for avoiding disease while travelling from: www.nathnac.org

The handbook, *Health Information for Overseas Travel* (2010), which draws together essential information for *healthcare professionals* regarding health advice for travellers, can also be obtained from this website.

Immunisation requirements change from time to time, and information on the current requirements for any particular country may be obtained from the embassy or legation of the appropriate country or from:

National Travel Health Network and Centre
UCLH NHS Foundation Trust
3rd Floor Central
250 Euston Road
London, NW1 2PG
Tel: 0845 602 6712
(8.30–11.45 a.m., 1–3.15 p.m. weekdays for health-care professionals **only**)
www.nathnac.org

Travel Medicine Team
Health Protection Scotland
Meridan Court
5 Cadogan Street
Glasgow, G2 6QE
Tel: (0141) 300 1130
(2–4 p.m. Monday and Wednesday, 9.30–11.30 a.m. Friday; for registered TRAVAX users **only**)
www.travax.nhs.uk (free for NHS Scotland users, registration required; subscription fee may be payable for users outside NHS Scotland)

Welsh Assembly Government
Tel: (029) 2082 5397
(9 a.m.–5.30 p.m. weekdays)

Department of Health, Social Services and Public Safety
Castle Buildings
Stormont
Belfast, BT4 3SQ
Tel: (028) 9052 2118 (9 a.m.–5 p.m. weekdays)
www.dhsspsni.gov.uk

15 Anaesthesia

15.1	General anaesthesia	634
15.1.1	Intravenous anaesthetics	635
15.1.2	Inhalational anaesthetics	638
15.1.3	Antimuscarinic drugs	640
15.1.4	Sedative and analgesic peri-operative drugs	642
15.1.4.1	Benzodiazepines	642
15.1.4.2	Non-opioid analgesics	645
15.1.4.3	Opioid analgesics	645
15.1.4.4	Other drugs for sedation	647
15.1.5	Neuromuscular blocking drugs	647
15.1.6	Drugs for reversal of neuromuscular blockade	651
15.1.7	Antagonists for central and respiratory depression	652
15.1.8	Drugs for malignant hyperthermia	654
15.2	Local anaesthesia	654

15.1 General anaesthesia

15.1.1	Intravenous anaesthetics
15.1.2	Inhalational anaesthetics
15.1.3	Antimuscarinic drugs
15.1.4	Sedative and analgesic peri-operative drugs
15.1.5	Neuromuscular blocking drugs
15.1.6	Drugs for reversal of neuromuscular blockade
15.1.7	Antagonists for central and respiratory depression
15.1.8	Drugs for malignant hyperthermia

Important

The drugs in section 15.1 should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

Several different types of drug are given together during general anaesthesia. Anaesthesia is induced with either a volatile drug given by inhalation (section 15.1.2) or with an intravenously administered drug (section 15.1.1); anaesthesia is maintained with an intravenous or inhalational anaesthetic. Analgesics (section 15.1.4), usually short-acting opioids, are also used. The use of neuromuscular blocking drugs (section 15.1.5) necessitates intermittent positive-pressure ventilation. Following surgery, anticholinesterases (section 15.1.6) can be given to reverse the effects of neuromuscular blocking drugs; specific antagonists (section 15.1.7) can be used to reverse central and respiratory depression caused by some drugs used in surgery. A topical local anaesthetic (section 15.2) can be used to reduce pain at the injection site.

Individual requirements vary considerably and the recommended doses are only a guide. Smaller doses are indicated in ill, shocked, or debilitated children and in significant hepatic impairment, while robust individuals may require larger doses. The required dose of induction agent may be less if the patient has been premedicated with a sedative agent (section 15.1.4) or if an opioid analgesic has been used.

Surgery and long-term medication The risk of losing disease control on stopping long-term medication before surgery is often greater than the risk posed by continuing it during surgery. It is vital that the anaesthetist knows about all drugs that a child is (or has been) taking.

Children with adrenal atrophy resulting from long-term corticosteroid use (section 6.3.2) may suffer a precipitous fall in blood pressure unless corticosteroid cover is

provided during anaesthesia and in the immediate postoperative period. Anaesthetists must therefore know whether a child is, or has been, receiving corticosteroids (including high-dose inhaled corticosteroids).

Other drugs that should normally not be stopped before surgery include drugs for epilepsy, asthma, immunosuppression, and metabolic, endocrine and cardiovascular disorders (but see potassium sparing diuretics, below). Expert advice is required for children receiving antivirals for HIV infection. For general advice on surgery in children with diabetes, see section 6.1.1.

Children taking antiplatelet medication or an oral anticoagulant present an increased risk for surgery. In these circumstances, the anaesthetist and surgeon should assess the relative risks and decide jointly whether the antiplatelet or the anticoagulant drug should be stopped or replaced with unfractionated or low molecular weight heparin therapy.

Drugs that should be stopped before surgery include combined oral contraceptives (see Surgery, section 7.3.1 for details). If antidepressants need to be stopped, they should be withdrawn gradually to avoid withdrawal symptoms. Tricyclic antidepressants need not be stopped, but there may be an increased risk of arrhythmias and hypotension (and dangerous interactions with vasopressor drugs); therefore, the anaesthetist should be informed if they are not stopped. Lithium should be stopped 24 hours before major surgery but the normal dose can be continued for minor surgery (with careful monitoring of fluids and electrolytes). Potassium-sparing diuretics may need to be withheld on the morning of surgery because hyperkalaemia may develop if renal perfusion is impaired or if there is tissue damage. Herbal medicines may be associated with adverse effects when given with anaesthetic drugs and consideration should be given to stopping them before surgery.

Anaesthesia and skilled tasks Children and their carers should be very carefully warned about the risk of undertaking skilled tasks after the use of sedatives and analgesics during minor outpatient procedures. For intravenous benzodiazepines and for a short general anaesthetic the risk extends to **at least 24 hours** after administration. Responsible persons should be available to take children home. The dangers of taking alcohol should also be emphasised.

Prophylaxis of acid aspiration Regurgitation and aspiration of gastric contents (Mendelson's syndrome) can be a complication of general anaesthesia, particularly in obstetrics and in gastro-oesophageal reflux disease; prophylaxis against acid aspiration is not routinely used in children but may be required in high-risk cases.

An **H₂-receptor antagonist** (section 1.3.1) can be used before surgery to increase the pH and reduce the volume of gastric fluid. It does not affect the pH of fluid already in the stomach and this limits its value in emergency procedures; an oral H₂-receptor antagonist can be given 1–2 hours before the procedure.

Anaesthesia, sedation, and resuscitation in dental practice

For details see *A Conscious Decision: A review of the use of general anaesthesia and conscious sedation in primary dental care*; report by a group chaired by the Chief Medical Officer and Chief Dental Officer, July 2000 and associated documents. Further details can also be found in *Conscious Sedation in the Provision of Dental Care*; report of an Expert Group on Sedation for Dentistry (commissioned by the Department of Health), 2003.

Guidance is also included in *Conscious Sedation in Dentistry: Dental Clinical Guidance*, Scottish Dental Clinical Effectiveness Programme, June 2012 (www.sdcep.org.uk).

15.1.1 Intravenous anaesthetics

Important

The drugs in this section should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

Intravenous anaesthetics may be used either to induce anaesthesia or for maintenance of anaesthesia throughout surgery. Intravenous anaesthetics nearly all produce their effect in one arm-brain circulation time and can cause apnoea and hypotension, and so adequate resuscitative facilities **must** be available. They are **contraindicated** if the anaesthetist is not confident of being able to maintain the airway. Extreme care is required in surgery of the mouth, pharynx, or larynx and in children with acute circulatory failure (shock) or fixed cardiac output.

To facilitate tracheal intubation, induction is usually followed by a neuromuscular blocking drug (section 15.1.5) or a short-acting opioid (section 15.1.4.3).

The doses of all intravenous anaesthetic drugs should be titrated according to response (except when using 'rapid sequence induction'). The doses and rates of administration should be reduced in those with hypovolaemia or cardiovascular disease; reduced doses may also be required in premedicated children.

Total intravenous anaesthesia This is a technique in which surgery is carried out with all drugs given intravenously. Respiration can be spontaneous, or controlled with oxygen-enriched air. Neuromuscular blocking drugs can be used to provide relaxation and prevent reflex muscle movements. The main problem to be overcome is the assessment of depth of anaesthesia. Target Controlled Infusion (TCI) systems can be used to titrate intravenous anaesthetic infusions to predicted plasma-drug concentrations; specific models with paediatric pharmacokinetic data should be used for children.

Anaesthesia and skilled tasks See section 15.1.

Drugs used for intravenous anaesthesia Propofol, the most widely used intravenous anaesthetic, can be used for induction or maintenance of anaesthesia in children, but it is not commonly used in neonates.

Propofol is associated with rapid recovery and less hangover effect than other intravenous anaesthetics. It causes pain on intravenous injection which can be reduced by intravenous lidocaine. Significant extraneous muscle movements can occur. Rarely, convulsions, anaphylaxis, and delayed recovery from anaesthesia can occur after propofol administration; the onset of convulsions can be delayed. Propofol is associated with bradycardia, occasionally profound; intravenous administration of an antimuscarinic drug is used to treat this.

Propofol can be used for sedation during diagnostic procedures but is contra-indicated in children under 16 years receiving intensive care because of the risk of propofol infusion syndrome (potentially fatal effects, including metabolic acidosis, arrhythmias, cardiac failure, rhabdomyolysis, hyperlipidaemia, hyperkalaemia, hepatomegaly, and renal failure).

Thiopental sodium is a barbiturate that is used for induction of anaesthesia, but it has no analgesic properties. Induction is generally smooth and rapid, but dose-related cardiorespiratory depression can occur. Awakening from a moderate dose of thiopental is rapid because the drug redistributes into other tissues, particularly fat. However, metabolism is slow and sedative effects can persist for 24 hours. Repeated doses have a cumulative effect particularly in neonates, and recovery is much slower.

Etomidate is an intravenous agent associated with rapid recovery without a hangover effect. Etomidate causes less hypotension than thiopental and propofol during induction. It produces a high incidence of extraneous muscle movements, which can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction. Pain on injection can be reduced by injecting into a larger vein or by giving an opioid analgesic just before induction. Etomidate suppresses adrenocortical function, particularly on continuous administration, and it should not be used for maintenance of anaesthesia. It should be used with caution in patients with underlying adrenal insufficiency, for example, those with sepsis.

Ketamine causes less hypotension than thiopental and propofol during induction. It is sometimes used in children requiring repeat anaesthesia (such as for serial burns dressings), however recovery is relatively slow and there is a high incidence of extraneous muscle movements. Ketamine can cause hallucinations, nightmares, and other transient psychotic effects; these can be reduced by a benzodiazepine, such as diazepam or midazolam.

mias, hypertension, hiccups, cough, phlebitis; AV block, cardiac arrest, respiratory depression, seizures, shivering, and Stevens-Johnson syndrome also reported

Licensed use *Hypnomidate*® licensed for use in children (age range not specified by manufacturer); *Etomidate-Lipuro*® not licensed for children under 6 months except for imperative indications during inpatient treatment.

Indications and dose

Induction of anaesthesia

• By slow intravenous injection

- **Child 1 month–18 years** 150–300 micrograms/kg (max. total dose 60 mg); child under 15 years may need up to 400 micrograms/kg (max. total dose 60 mg)

Important Administer over 30–60 seconds (60 seconds for children in whom hypotension might be hazardous)

Note Doses in *BNF for Children* may differ from those in the product literature

Etomidate-Lipuro® (B. Braun) (PoM)

Injection (emulsion), etomidate 2 mg/mL, net price 10-mL amp = £1.56

Hypnomidate® (Janssen) (PoM)

Injection, etomidate 2 mg/mL, net price 10-mL amp = £1.38

Excipients include propylene glycol (see Excipients, p. 2)

KETAMINE

Cautions see notes above; dehydration; hypertension; respiratory tract infection; increased cerebrospinal fluid pressure; predisposition to seizures, hallucinations, or nightmares; psychotic disorders; head injury or intracranial mass lesions; thyroid dysfunction; raised intraocular pressure; **interactions:** Appendix 1 (anaesthetics, general)

Contra-indications see notes above; hypertension, pre-eclampsia or eclampsia, severe cardiac disease, stroke; raised intracranial pressure; head trauma; acute porphyria (section 9.8.2)

Hepatic impairment consider dose reduction

Pregnancy may depress neonatal respiration if used during delivery

Breast-feeding avoid for at least 12 hours after last dose

Side-effects see notes above; also nausea, vomiting, tachycardia, hypertension, diplopia, nystagmus, rash; *less commonly* arrhythmias, hypotension, bradycardia, respiratory depression, laryngospasm; *rarely* hypersalivation, apnoea, insomnia, cystitis (including haemorrhagic); *also reported* raised intra-ocular pressure

Indications and dose

Sedation prior to invasive or painful procedures

• By intravenous injection

- **Child 1 month–18 years** 1–2 mg/kg as a single dose

Induction and maintenance of anaesthesia (short procedures)

• By intravenous injection over at least 60 seconds

- **Neonate** 1–2 mg/kg produces 5–10 minutes of surgical anaesthesia, adjusted according to response

- **Child 1 month–12 years** 1–2 mg/kg produces 5–10 minutes of surgical anaesthesia, adjusted according to response

ETOMIDATE

Cautions see notes above; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (anaesthetics, general)

Contra-indications see notes above

Hepatic impairment reduce dose in liver cirrhosis

Pregnancy may depress neonatal respiration if used during delivery

Breast-feeding breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia

Side-effects see notes above; also nausea, vomiting, hypotension, apnoea, hyperventilation, stridor, rash; *less commonly* hypersalivation, bradycardia, arrhyth-

Child 12–18 years 1–4.5 mg/kg adjusted according to response (2 mg/kg usually produces 5–10 minutes of surgical anaesthesia)

- By intramuscular injection

Neonate 4 mg/kg usually produces 15 minutes of surgical anaesthesia, adjusted according to response

Child 1 month–18 years 4–13 mg/kg (4 mg/kg sufficient for some diagnostic procedures), adjusted according to response; 10 mg/kg usually produces 12–25 minutes of surgical anaesthesia

Induction and maintenance of anaesthesia (longer procedures)

- By intravenous administration

Neonate initially 0.5–2 mg/kg by intravenous injection, followed by a continuous intravenous infusion of 8 micrograms/kg/minute adjusted according to response; up to 30 micrograms/kg/minute may be used to produce deep anaesthesia

Child 1 month–18 years initially 0.5–2 mg/kg by intravenous injection followed by a continuous intravenous infusion of 10–45 micrograms/kg/minute adjusted according to response

Administration for continuous intravenous infusion, dilute to a concentration of 1 mg/mL with Glucose 5% or Sodium Chloride 0.9%; use microdrip infusion for maintenance of anaesthesia

For intravenous injection, dilute 100 mg/mL strength to a concentration of not more than 50 mg/mL with Glucose 5% or Sodium Chloride 0.9%

Ketalar® (Pfizer) (CD4+1)

Injection, ketamine (as hydrochloride) 10 mg/mL, net price 20-mL vial = £5.06; 50 mg/mL, 10-mL vial = £8.77; 100 mg/mL, 10-mL vial = £16.10

Note 100 mg/mL, 10-mL vial may be difficult to obtain

PROPOFOL

Cautions see notes above; cardiac impairment; respiratory impairment; hypovolaemia; epilepsy; hypotension; raised intracranial pressure; monitor blood-lipid concentration if risk of fat overload or if sedation longer than 3 days; **interactions:** Appendix 1 (anaesthetics, general)

Contra-indications see notes above

Hepatic impairment use with caution

Renal impairment use with caution

Pregnancy may depress neonatal respiration if used during delivery; max. dose for maintenance of anaesthesia, 6 mg/kg/hour

Breast-feeding breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia

Side-effects see notes above; also hypotension, tachycardia, transient apnoea, headache; *less commonly* thrombosis, phlebitis; *rarely* arrhythmia, euphoria; *very rarely* pancreatitis, pulmonary oedema, sexual disinhibition, and discoloration of urine; propofol infusion syndrome (potentially fatal effects, including metabolic acidosis, arrhythmias, cardiac failure, rhabdomyolysis, hyperlipidaemia, hyperkalaemia, hepatomegaly, and renal failure) reported with prolonged infusion of doses exceeding 4 mg/kg/hour

Indications and dose

Induction of anaesthesia using 0.5% or 1% injection

- By slow intravenous injection or by intravenous infusion

Child 1 month–18 years adjust dose according to age, body-weight, and response; usual dose in child 1 month–17 years 2.5–4 mg/kg; usual dose in child 17–18 years 1.5–2.5 mg/kg at a rate of 20–40 mg every 10 seconds until response

Induction of anaesthesia using 2% injection

- By intravenous infusion

Child 3–18 years adjust dose according to age, body-weight, and response; usual dose in child 3–17 years 2.5–4 mg/kg; usual dose in child 17–18 years 1.5–2.5 mg/kg at a rate of 20–40 mg every 10 seconds until response

Maintenance of anaesthesia using 1% injection

- By continuous intravenous infusion

Child 1 month–18 years adjust dose according to age, body-weight, and response; usual dose in child 1 month–17 years 9–15 mg/kg/hour; usual dose in child 17–18 years 4–12 mg/kg/hour, adjusted according to response

Maintenance of anaesthesia using 2% injection

- By continuous intravenous infusion

Child 3–18 years adjust dose according to age, body-weight, and response; usual dose in child 3–17 years 9–15 mg/kg/hour; usual dose in child 17–18 years 4–12 mg/kg/hour, adjusted according to response

Sedation of ventilated children in intensive care using 1% or 2% injection

- By continuous intravenous infusion

Child 16–18 years 0.3–4 mg/kg/hour, adjusted according to response

Induction of sedation for surgical and diagnostic procedures using 0.5% or 1% injection

- By slow intravenous injection

Child 1 month–18 years dose and rate of administration adjusted according to desired level of sedation and response; usual dose in child 1 month–17 years 1–2 mg/kg; usual dose in child 17–18 years 0.5–1 mg/kg over 1–5 minutes

Maintenance of sedation for surgical and diagnostic procedures using 0.5% injection

- By intravenous infusion

Child 17–18 years dose and rate of administration adjusted according to desired level of sedation and response; usual dose 1.5–4.5 mg/kg/hour (additionally, if rapid increase in sedation required, by slow intravenous injection 10–20 mg)

Maintenance of sedation for surgical and diagnostic procedures using 1% injection

- By intravenous infusion

Child 1 month–18 years dose and rate of administration adjusted according to desired level of sedation and response; usual dose in child 1 month–17 years 1.5–9 mg/kg/hour (addition-

ally, if rapid increase in sedation required, *by slow intravenous injection*, max. 1 mg/kg; usual dose in child 17–18 years 1.5–4.5 mg/kg/hour (additionally, if rapid increase in sedation required, *by slow intravenous injection*, 10–20 mg)

Maintenance of sedation for surgical and diagnostic procedures using 2% injection

• By intravenous infusion

Child 3–18 years dose and rate of administration adjusted according to desired level of sedation and response; usual dose in child 3–17 years 1.5–9 mg/kg/hour; usual dose in child 17–18 years 1.5–4.5 mg/kg/hour (additionally, if rapid increase in sedation required, *by slow intravenous injection* using 0.5% or 1% injection, 10–20 mg)

Administration shake before use; microbiological filter not recommended; may be administered via a Y-piece close to injection site co-administered with Glucose 5% or Sodium chloride 0.9%

0.5% emulsion for injection or infusion; may be administered undiluted, or diluted with Glucose 5% or Sodium chloride 0.9%; dilute to a concentration not less than 1 mg/mL

1% emulsion for injection or infusion; may be administered undiluted, or diluted with Glucose 5% (*Diprivan*® or *Propofol-Lipuro*®) or Sodium chloride 0.9% (*Propofol-Lipuro*® only); dilute to a concentration not less than 2 mg/mL; use within 6 hours of preparation

2% emulsion for infusion; do not dilute

Propofol (Non-proprietary) (PoM)

0.5% injection (emulsion), propofol 5 mg/mL, net price 20-mL amp = £3.46

Brands include *Propofol-Lipuro*®

1% injection (emulsion), propofol 10 mg/mL, net price 20-mL amp = £4.18, 50-mL bottle = £10.10, 100-mL bottle = £19.40

Brands include *Propofol-Lipuro*®, *Propoven*®

2% injection (emulsion), propofol 20 mg/mL, net price 50-mL vial = £21.30

Brands include *Propofol-Lipuro*®, *Propoven*®

Diprivan® (AstraZeneca) (PoM)

1% injection (emulsion), propofol 10 mg/mL, net price 20-mL amp = £3.07, 50-mL prefilled syringe (for use with *Diprifusor*® TCI system) = £10.68

2% injection (emulsion), propofol 20 mg/mL, net price 50-mL prefilled syringe (for use with *Diprifusor*® TCI system) = £15.16

THIOPENTAL SODIUM

(Thiopentone sodium)

Cautions see notes above; cardiovascular disease; reconstituted solution is highly alkaline—extravasation causes tissue necrosis and severe pain; avoid intra-arterial injection; **interactions:** Appendix 1 (anaesthetics, general)

Contra-indications see notes above; acute porphyria (section 9.8.2); myotonic dystrophy

Hepatic impairment use with caution—reduce dose

Renal impairment caution in severe impairment

Pregnancy may depress neonatal respiration when used during delivery

Breast-feeding breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia

Side-effects hypotension, arrhythmias, myocardial depression, laryngeal spasm, cough, headache, sneezing, hypersensitivity reactions, rash

Licensed use not licensed for use in status epilepticus; not licensed for use by intravenous infusion

Indications and dose

Induction of anaesthesia

• By slow intravenous injection

Neonate initially up to 2 mg/kg, then 1 mg/kg repeated as necessary (max. total dose 4 mg/kg)

Child 1 month–18 years initially up to 4 mg/kg, then 1 mg/kg repeated as necessary (max. total dose 7 mg/kg)

Prolonged status epilepticus

• By slow intravenous injection and intravenous infusion

Neonate initially up to 2 mg/kg by *intravenous injection*, then up to 8 mg/kg/hour by *continuous intravenous infusion*, adjusted according to response

Child 1 month–18 years initially up to 4 mg/kg by *intravenous injection*, then up to 8 mg/kg/hour by *continuous intravenous infusion*, adjusted according to response

Administration For *intravenous injection*, reconstitute 500-mg vial with 20 mL Water for Injections to give 25 mg/mL solution; give over at least 10–15 seconds; for *intravenous infusion* reconstituted solution may be further diluted with Sodium Chloride 0.9%

Thiopental (Archimedes) (PoM)

Injection, powder for reconstitution, thiopental sodium, net price 500-mg vial = £5.75

15.1.2 Inhalational anaesthetics

Important

The drugs in this section should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

Inhalational anaesthetics include gases and volatile liquids. *Gaseous anaesthetics* require suitable equipment for administration. *Volatile liquid anaesthetics* are administered using calibrated vaporisers, using air, oxygen, or nitrous oxide-oxygen mixtures as the carrier gas. To prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times. Higher concentrations of oxygen (greater than 30%) are usually required during inhalational anaesthesia with nitrous oxide, see Nitrous Oxide, p. 640.

Anaesthesia and skilled tasks See section 15.1.

Volatile liquid anaesthetics

Volatile liquid anaesthetics can be used for induction and maintenance of anaesthesia, and following induction with an intravenous anaesthetic (section 15.1.1).

Volatile liquid anaesthetics can trigger malignant hyperthermia (section 15.1.8) and are contra-indicated in those susceptible to malignant hyperthermia. They can increase cerebrospinal pressure and should be

used with caution in those with raised intracranial pressure. They can also cause hepatotoxicity in those who are sensitised to halogenated anaesthetics. In children with neuromuscular disease, inhalational anaesthetics are very rarely associated with hyperkalaemia, resulting in cardiac arrhythmias and death. Cardiorespiratory depression, hypotension, and arrhythmias are common side-effects of volatile liquid anaesthetics; convulsions have also been reported. They may also cause mood changes that can last for several days.

Isoflurane is a volatile liquid anaesthetic. Heart rhythm is generally stable during isoflurane anaesthesia, but heart-rate can rise. Systemic arterial pressure and cardiac output can fall, owing to a decrease in systemic vascular resistance. Muscle relaxation occurs and the effects of muscle relaxant drugs are potentiated. Isoflurane can irritate mucous membranes, causing cough, breath-holding, and laryngospasm. Isoflurane is the preferred inhalational anaesthetic for use in obstetrics.

Desflurane is a rapid-acting volatile liquid anaesthetic; it is reported to have about one-fifth the potency of isoflurane. Emergence and recovery from anaesthesia are particularly rapid because of its low solubility. Desflurane is not recommended for induction of anaesthesia as it is irritant to the upper respiratory tract; cough, breath-holding, apnoea, laryngospasm, and increased secretions can occur.

Sevoflurane is a rapid-acting volatile liquid anaesthetic and is more potent than desflurane. Emergence and recovery are particularly rapid but slower than desflurane. Sevoflurane is non-irritant and is therefore used for inhalational induction of anaesthesia. Sevoflurane can interact with carbon dioxide absorbents to form compound A, a potentially nephrotoxic vinyl ether. However, in spite of extensive use, no cases of sevoflurane-induced permanent renal injury have been reported and the carbon dioxide absorbents used in the UK produce very low concentrations of compound A, even in low-flow anaesthetic systems.

DESFLURANE

Cautions see notes above; **interactions:** Appendix 1 (anaesthetics, general)

Contra-indications see notes above

Pregnancy may depress neonatal respiration if used during delivery

Breast-feeding breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia

Side-effects see notes above

Indications and dose

Induction of anaesthesia

- By inhalation through specifically calibrated vaporiser
- Child 12–18 years** 4–11%, but not recommended (see notes above)

Maintenance of anaesthesia

- By inhalation through specifically calibrated vaporiser
- Neonate** 2–6% in nitrous oxide-oxygen; 2.5–8.5% in oxygen or oxygen-enriched air
- Child 1 month–18 years** 2–6% in nitrous oxide-oxygen; 2.5–8.5% in oxygen or oxygen-enriched air

ISOFLURANE

Cautions see notes above; **interactions:** Appendix 1 (anaesthetics, general)

Contra-indications see notes above

Pregnancy may depress neonatal respiration if used during delivery

Breast-feeding breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia

Side-effects see notes above

Indications and dose

Induction of anaesthesia

- By inhalation through specifically calibrated vaporiser
- Neonate** increased gradually according to response from 0.5–3% in oxygen or nitrous oxide-oxygen
- Child 1 month–18 years** increased gradually according to response from 0.5–3% in oxygen or nitrous oxide-oxygen

Maintenance of anaesthesia

- By inhalation through specifically calibrated vaporiser
- Neonate** 1–2.5% in nitrous oxide-oxygen; additional 0.5–1% may be required if given with oxygen alone
- Child 1 month–18 years** 1–2.5% in nitrous oxide-oxygen; additional 0.5–1% may be required if given with oxygen alone; caesarean section, 0.5–0.75% in nitrous oxide-oxygen

SEVOFLURANE

Cautions see notes above; susceptibility to QT-interval prolongation; **interactions:** Appendix 1 (anaesthetics, general)

Contra-indications see notes above

Renal impairment use with caution

Pregnancy may depress neonatal respiration if used during delivery

Breast-feeding breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia

Side-effects see notes above; also urinary retention, leucopenia, agitation, cardiac arrest, torsade de pointes, and dystonia also reported

Indications and dose

Induction of anaesthesia

- By inhalation through specifically calibrated vaporiser
- Neonate** up to 4% in oxygen or nitrous oxide-oxygen, according to response
- Child 1 month–18 years** initially 0.5–1% then increased gradually up to 8% in oxygen or nitrous oxide-oxygen, according to response

Maintenance of anaesthesia

- By inhalation through specifically calibrated vaporiser
- Neonate** 0.5–2% in oxygen or nitrous oxide-oxygen, according to response
- Child 1 month–18 years** 0.5–3% in oxygen or nitrous oxide-oxygen, according to response

Nitrous oxide

Nitrous oxide is used for maintenance of anaesthesia and, in sub-anaesthetic concentrations, for analgesia. For *anaesthesia* it is commonly used in a concentration of 50 to 66% in oxygen as part of a balanced technique in association with other inhalational or intravenous agents. Nitrous oxide is unsatisfactory as a sole anaesthetic owing to lack of potency, but is useful as part of a combination of drugs since it allows a significant reduction in dosage.

For *analgesia* (without loss of consciousness) a mixture of nitrous oxide and oxygen containing 50% of each gas (*Entonox*®, *Equanox*®) is used. Self-administration using a demand valve may be used in children who are able to self-regulate their intake (usually over 5 years of age) for painful dressing changes, as an aid to postoperative physiotherapy, for wound debridement and in emergency ambulances.

Nitrous oxide may have a deleterious effect if used in children with an air-containing closed space since nitrous oxide diffuses into such a space with a resulting increase in pressure. This effect may be dangerous in conditions such as pneumothorax, which may enlarge to compromise respiration, or in the presence of intracranial air after head injury, entrapped air following recent underwater dive, or recent intra-ocular gas injection.

Hypoxia can occur immediately following the administration of nitrous oxide; additional oxygen should always be given for several minutes after stopping the flow of nitrous oxide.

Exposure of children to nitrous oxide for prolonged periods, either by continuous or by intermittent administration, may result in megaloblastic anaemia owing to interference with the action of vitamin B₁₂; neurological toxic effects can occur without preceding overt haematological changes. For the same reason, exposure of theatre staff to nitrous oxide should be minimised. Depression of white cell formation may also occur.

Assessment of plasma-vitamin B₁₂ concentration should be considered before nitrous oxide anaesthesia in children at risk of deficiency, including children who have a poor, vegetarian, or vegan diet and children with a history of anaemia. Nitrous oxide should **not** be given continuously for longer than 24 hours or more frequently than every 4 days without close supervision and haematological monitoring.

NITROUS OXIDE

Cautions see notes above; **interactions:** Appendix 1 (anaesthetics, general)

Pregnancy may depress neonatal respiration if used during delivery

Breast-feeding breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia

Side-effects see notes above

Indications and dose

Maintenance of anaesthesia in conjunction with other anaesthetic agents

- By inhalation using suitable anaesthetic apparatus

Neonate 50–66% in oxygen

Child 1 month–18 years 50–66% in oxygen

Analgesia

- By inhalation using suitable anaesthetic apparatus

(see also notes above)

Neonate up to 50% in oxygen, according to the child's needs

Child 1 month–18 years up to 50% in oxygen, according to the child's needs

15.1.3 Antimuscarinic drugs

Important

The drugs in this section should only be administered by, or under the direct supervision of, personnel experienced in their use.

Antimuscarinic drugs are used (less commonly nowadays) as premedicants to dry bronchial and salivary secretions which are increased by intubation, upper airway surgery, or some inhalational anaesthetics, but they should not be used for this indication in children with cystic fibrosis. Antimuscarinics are also used before or with neostigmine (section 15.1.6) to prevent bradycardia, excessive salivation, and other muscarinic actions of neostigmine. They also prevent bradycardia and hypotension associated with drugs such as propofol and suxamethonium.

Atropine sulfate is now rarely used for premedication but still has an emergency role in the treatment of vagotonic side-effects. For its role in cardiopulmonary resuscitation, see section 2.7.3.

Hyoscine hydrobromide reduces secretions and also provides a degree of amnesia, sedation, and anti-emesis. Unlike atropine it may produce bradycardia rather than tachycardia. In some children hyoscine may cause the central anticholinergic syndrome (excitement, ataxia, hallucinations, behavioural abnormalities, and drowsiness).

Glycopyrronium bromide reduces salivary secretions. When given intravenously it produces less tachycardia than atropine. It is widely used with neostigmine for reversal of non-depolarising muscle relaxants (section 15.1.5).

Glycopyrronium or hyoscine hydrobromide are also used to control excessive secretions in upper airways or hypersalivation in palliative care and in children unable to control posture or with abnormal swallowing reflex; effective dose varies and tolerance may develop. The intramuscular route should be avoided if possible. Hyoscine transdermal patches may also be used (section 4.6).

ATROPINE SULFATE

Cautions see notes in section 1.2

Duration of action Since atropine has a shorter duration of action than neostigmine, late unopposed bradycardia may result; close monitoring of the patient is necessary

Contra-indications see notes in section 1.2

Pregnancy not known to be harmful; manufacturer advises caution

Breast-feeding small amount present in milk—manufacturer advises caution

Side-effects see notes in section 1.2

Licensed use not licensed for use by oral route; not licensed for use in children under 12 years for intra-operative bradycardia; not licensed for use in children under 12 years by intravenous route for premedication; not licensed for the control of muscarinic side-effects of edrophonium in reversal of competitive neuromuscular block

Indications and dose

Premedication

- By mouth 1–2 hours before induction of anaesthesia

Neonate 20–40 micrograms/kg

Child 1 month–18 years 20–40 micrograms/kg (max. 900 micrograms)

- By intravenous injection immediately before induction of anaesthesia

Neonate 10 micrograms/kg

Child 1 month–12 years 20 micrograms/kg (minimum 100 micrograms, max. 600 micrograms)

Child 12–18 years 300–600 micrograms

- By subcutaneous or intramuscular injection 30–60 minutes before induction of anaesthesia

Neonate 10 micrograms/kg

Child 1 month–12 years 10–30 micrograms/kg (minimum 100 micrograms, max. 600 micrograms)

Child 12–18 years 300–600 micrograms

Intra-operative bradycardia

- By intravenous injection

Neonate 10–20 micrograms/kg

Child 1 month–12 years 10–20 micrograms/kg

Child 12–18 years 300–600 micrograms (larger doses in emergencies)

Control of muscarinic side-effects of neostigmine 50 micrograms/kg in reversal of competitive neuromuscular block

- By intravenous injection

Neonate 20 micrograms/kg

Child 1 month–12 years 20 micrograms/kg (max. 1.2 mg)

Child 12–18 years 0.6–1.2 mg

Control of muscarinic side-effects of edrophonium in reversal of competitive neuromuscular block

- By intravenous injection

Child 1 month–18 years 7 micrograms/kg (max. 600 micrograms)

Cycloplegia, anterior uveitis (section 11.5)

Administration for administration *by mouth*, injection solution may be given orally

¹Atropine (Non-proprietary) (PoM)


Injection, atropine sulfate 600 micrograms/mL, net price 1-mL amp = 86p

Note Other strengths also available

Injection, prefilled disposable syringe, atropine sulfate 100 micrograms/mL, net price 5 mL = £4.58, 10 mL = £5.39, 30 mL = £8.95

Injection, prefilled disposable syringe, atropine sulfate 200 micrograms/mL, net price 5 mL = £6.78; 300 micrograms/mL, 10 mL = £6.47; 600 micrograms/mL, 1 mL = £6.78

Oral solution, atropine sulfate 100 micrograms/mL available from 'special-order' manufacturers or specialist importing companies, see p. 840

Tablets , atropine sulfate 600 micrograms, net price 28-tab pack = £23.80

¹Minijet® Atropine (UCB Pharma) (PoM)

Injection, atropine sulfate 100 micrograms/mL, net price 5 mL = £6.34, 10 mL = £7.11, 30 mL = £11.19

GLYCOPYRROLIUM BROMIDE (Glycopyrrolate)

Cautions see notes in section 1.2 (Antimuscarinics)

Contra-indications see notes in section 1.2 (Antimuscarinics)

Side-effects see notes in section 1.2 (Antimuscarinics)

Licensed use not licensed for use in control of upper airways secretion and hypersalivation

Indications and dose

Premedication at induction

- By intravenous or intramuscular injection

Neonate 5 micrograms/kg

Child 1 month–12 years 4–8 micrograms/kg (max. 200 micrograms)

Child 12–18 years 200–400 micrograms or 4–5 micrograms/kg (max. 400 micrograms)

Intra-operative bradycardia

- By intravenous injection

Neonate 10 micrograms/kg, repeated if necessary

Child 1 month–18 years 4–8 micrograms/kg (max. 200 micrograms), repeated if necessary

Control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block

- By intravenous injection

Neonate 10 micrograms/kg

Child 1 month–12 years 10 micrograms/kg (max. 500 micrograms)

Child 12–18 years 200 micrograms per 1 mg of neostigmine, or 10–15 micrograms/kg

Control of upper airways secretion and hypersalivation

- By mouth

Child 1 month–18 years 40–100 micrograms/kg (max. 2 mg) 3–4 times daily, adjusted according to response

- By subcutaneous infusion

Child 1 month–12 years 12–40 micrograms/kg/24 hours (max. 1.2 mg)

Child 12–18 years 0.6–1.2 mg/24 hours

- By subcutaneous injection or intramuscular injection or intravenous injection (but see notes above)

Child 1 month–12 years 4–10 micrograms/kg (max. 200 micrograms) 4 times a day when required

Child 12–18 years 200 micrograms every 4 hours when required

1. (PoM) restriction does not apply where administration is for saving life in emergency

Administration for administration *by mouth*, injection solution may be given or crushed tablets suspended in water

Glycopyrronium bromide (Non-proprietary)

Injection, glycopyrronium bromide 200 micrograms/mL, net price 1-mL amp = 54p, 3-mL amp = £1.50

Tablets, glycopyrronium bromide 1 mg and 2 mg Available on a named-patient basis from specialist importing companies, p. 840

With neostigmine metilsulfate

Section 15.1.6

HYOSCINE HYDROBROMIDE (Scopolamine hydrobromide)

Cautions see notes in section 1.2 and notes above; also epilepsy

Contra-indications see notes in section 1.2

Hepatic impairment see Hyoscine Hydrobromide, section 4.6

Renal impairment see Hyoscine Hydrobromide, section 4.6

Pregnancy see Hyoscine Hydrobromide, section 4.6

Breast-feeding see Hyoscine Hydrobromide, section 4.6

Side-effects see notes in section 1.2

Indications and dose

Premedication

- By subcutaneous or intramuscular injection 30–60 minutes before induction
- Child 1–12 years** 15 micrograms/kg (max. 600 micrograms)
- Child 12–18 years** 200–600 micrograms

Note Same dose may be given by intravenous injection immediately before induction

Motion sickness, excessive respiratory secretions, hypersalivation associated with clozapine therapy section 4.6

Hyoscine (Non-proprietary) (PoM)

Injection, hyoscine hydrobromide 400 micrograms/mL, net price 1-mL amp = £2.88; 600 micrograms/mL, 1-mL amp = £2.53

Preparations

For transdermal and oral preparations see section 4.6

and provide some degree of pre-operative amnesia. The choice of drug depends on the individual child, the nature of the procedure, the anaesthetic to be used, and other prevailing circumstances such as outpatients, obstetrics, and recovery facilities. The choice also varies between elective and emergency procedures. Oral administration is preferred if possible; the rectal route should only be used in exceptional circumstances. Sedative premedication with benzodiazepines should be avoided in children with a compromised airway, CNS depression, or a history of sleep apnoea.

Premedicants can be given the night before major surgery; a further, smaller dose may be required the following morning if any delay in starting surgery is anticipated. Alternatively, the first dose may be given on the day of procedure.

Oral **midazolam** is the most common premedicant for children; **temazepam** may be used in older children. The antihistamine **alimemazine** (section 3.4.1) is occasionally used orally, but when given alone it may cause postoperative restlessness in the presence of pain.

Sedation for clinical procedures Sedation of children during diagnostic and therapeutic procedures is used to reduce fear and anxiety, to control pain, and to minimise excessive movement. The choice of sedative drug will depend upon the intended procedure and whether the child is cooperative; some procedures are safer and more successful under anaesthesia. The child should be **monitored carefully**; monitoring should begin as soon as the sedative is given or when the child becomes drowsy, and should be continued until the child wakes up.

Midazolam and **chloral hydrate** (section 4.1.1) are suitable for sedating children for painless procedures, such as imaging. For painful procedures, alternative choices include **nitrous oxide** (section 15.1.2), **local anaesthesia** (section 15.2), **ketamine** (section 15.1.1), or concomitant use of sedation with **opioid** or **non-opioid analgesia** (section 4.7).

Dental procedures Sedation for dental procedures should be limited to conscious sedation whenever possible. **Nitrous oxide** (section 15.1.2) alone and **midazolam** are effective for many children. For further information on hypnotics used for dental procedures, see p. 169.

Anaesthesia and skilled tasks See section 15.1.

15.1.4 Sedative and analgesic peri-operative drugs

15.1.4.1 Benzodiazepines

15.1.4.2 Non-opioid analgesics

15.1.4.3 Opioid analgesics

15.1.4.4 Other drugs for sedation

Important

The drugs in this section should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

Premedication Fear and anxiety before a procedure (including the night before) can be minimised by using a sedative drug, usually a **benzodiazepine**. Premedication may also augment the action of anaesthetics

15.1.4.1 Benzodiazepines

Benzodiazepines possess useful properties for premedication including relief of anxiety, sedation, and amnesia; short-acting benzodiazepines taken by mouth are the most common premedicants. Benzodiazepines are also used for sedation prior to clinical procedures and for sedation in intensive care.

Benzodiazepines may occasionally cause marked respiratory depression and facilities for its treatment are essential; flumazenil (section 15.1.7) is used to antagonise the effects of benzodiazepines.

Midazolam, a water-soluble benzodiazepine, is the preferred benzodiazepine for premedication and for sedation for clinical procedures in children. It has a fast onset of action, and recovery is faster than for other benzodiazepines. Recovery may be longer in

children with a low cardiac output, or after repeated dosing.

Midazolam can be given by mouth [unlicensed], but its bitter acidic taste may need to be disguised. It can also be given buccally [unlicensed indication] or intranasally [unlicensed]. Midazolam is associated with profound sedation when high doses are given or when it is used with certain other drugs. It can cause severe disinhibition and restlessness in some children. Midazolam is not recommended for prolonged sedation in neonates; drug accumulation is likely to occur

Overdosage with midazolam

There have been reports of overdosage in adults when high strength midazolam injection has been used for conscious sedation. The use of high strength midazolam (5 mg/mL in 2 mL and 10 mL ampoules, or 2 mg/mL in 5 mL ampoules) should be restricted to general anaesthesia, intensive care, palliative care, or other situations where the risk has been assessed. It is advised that flumazenil (section 15.1.7) is available where midazolam is used, to reverse the effects if necessary.

Temazepam is given by mouth for premedication in older children and has a short duration of action. Anxiolytic and sedative effects last about 90 minutes, although there may be residual drowsiness. Temazepam is rarely used for dental procedures in children.

Lorazepam produces more prolonged sedation than temazepam and it has marked amnesic effects.

Peri-operative use of **diazepam** is not recommended in children; onset and magnitude of response are unreliable, and paradoxical effects may occur. Diazepam is not used for dental procedures in children.

LORAZEPAM

Cautions see notes above and section 4.8.2; **interactions:** Appendix 1 (anxiolytics and hypnotics)

Contra-indications see Diazepam, section 4.8.2

Hepatic impairment see Benzodiazepines, section 4.8.1

Renal impairment see Benzodiazepines, section 4.8.1

Pregnancy see Benzodiazepines, section 4.8.1

Breast-feeding see Benzodiazepines, section 4.8.1

Side-effects see notes above and Diazepam, section 4.8.2

Licensed use not licensed for use in children under 5 years by mouth; not licensed for use in children under 12 years by intravenous injection

Indications and dose

Premedication

• By mouth

Child 1 month–12 years 50–100 micrograms/kg (max. 4 mg) at least 1 hour before procedure

Child 12–18 years 1–4 mg at least 1 hour before procedure

Note Same dose may be given the night before procedure in addition to, or to replace, dose before procedure

• By intravenous injection

Child 1 month–18 years 50–100 micrograms/kg (max. 4 mg)

Note Give intravenous injection 30–45 minutes before procedure

Status epilepticus section 4.8.2

Administration for *intravenous injection*, dilute injection solution with an equal volume of Sodium Chloride 0.9%; give over 3–5 minutes; max. rate 50 micrograms/kg over 3 minutes

Lorazepam (Non-proprietary) CD4-1

Tablets, lorazepam 1 mg, net price 28-tab pack = £2.45; 2.5 mg, 28-tab pack = £3.68. Label: 2 or 19

Injection, lorazepam 4 mg/mL, net price 1-mL amp = 35p

Excipients include benzyl alcohol (avoid in neonates unless there is no safer alternative available, see Excipients, p. 2), propylene glycol

Brands include Ativan®

MIDAZOLAM

Cautions see notes above; cardiac disease; respiratory disease; myasthenia gravis; neonates; history of drug or alcohol abuse; reduce dose if debilitated; risk of severe hypotension in children with hypovolaemia, vasoconstriction, hypothermia; avoid prolonged use (and abrupt withdrawal thereafter); **interactions:** Appendix 1 (anxiolytics and hypnotics)

Contra-indications marked neuromuscular respiratory weakness including unstable myasthenia gravis; severe respiratory depression; acute pulmonary insufficiency; sleep apnoea syndrome

Hepatic impairment use with caution; can precipitate coma

Renal impairment use with caution in chronic renal failure—increased cerebral sensitivity

Pregnancy avoid regular use (risk of neonatal withdrawal symptoms); use only if clear indication such as seizure control (high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression)

Breast-feeding small amount present in milk—avoid breast-feeding for 24 hours after administration (although amount probably too small to be harmful after single doses)

Side-effects see notes above; gastro-intestinal disturbances, dry mouth, hiccups, increased appetite, jaundice; hypotension, cardiac arrest, heart rate changes, anaphylaxis, thrombosis; laryngospasm, bronchospasm, respiratory depression and respiratory arrest (particularly with high doses or on rapid injection); drowsiness, confusion, ataxia, amnesia, headache, euphoria, hallucinations, convulsions (more common in neonates), fatigue, dizziness, vertigo, involuntary movements, paradoxical excitement and aggression, dysarthria; urinary retention, incontinence; blood disorders; muscle weakness; visual disturbances; salivation changes; skin reactions; injection-site reactions; with *intranasal administration* burning sensation, lacrimation, and severe irritation of nasal mucosa

Licensed use not licensed for use in children under 6 months for premedication and conscious sedation; not licensed for use by mouth; not licensed for use by buccal administration for conscious sedation

Indications and dose

Conscious sedation for procedures (but see notes above)

- By mouth

Child 1 month–18 years 500 micrograms/kg (max. 20 mg) 30–60 minutes before procedure

- By buccal administration

Child 6 months–10 years 200–300 micrograms/kg (max. 5 mg)

Child 10–18 years 6–7 mg (max. 8 mg if 70 kg or over)

- By rectum

Child 6 months–12 years 300–500 micrograms/kg 15–30 minutes before procedure

- By intravenous injection over 2–3 minutes 5–10 minutes before procedure

Child 1 month–6 years initially 25–50 micrograms/kg, increased if necessary in small steps (max. total dose 6 mg)

Child 6–12 years initially 25–50 micrograms/kg, increased if necessary in small steps (max. total dose 10 mg)

Child 12–18 years initially 25–50 micrograms/kg, increased if necessary in small steps (max. total dose 7.5 mg)

Premedication (but see notes above)

- By mouth

Child 1 month–18 years 500 micrograms/kg (max. 20 mg) 15–30 minutes before the procedure

- By rectum

Child 6 months–12 years 300–500 micrograms/kg 15–30 minutes before induction

Induction of anaesthesia (but rarely used)

- By slow intravenous injection

Child 7–18 years initially 150 micrograms/kg (max. 7.5 mg) given in steps of 50 micrograms/kg (max. 2.5 mg) over 2–5 minutes; wait for 2–5 minutes then give additional doses of 50 micrograms/kg (max. 2.5 mg) every 2 minutes if necessary; max. total dose 500 micrograms/kg (not exceeding 25 mg)

Sedation in intensive care

- By intravenous injection and continuous intravenous infusion

Neonate less than 32 weeks corrected gestational age 60 micrograms/kg/hour by continuous intravenous infusion, reduced after 24 hours to 30 micrograms/kg/hour; adjusted according to response; max. treatment duration 4 days

Neonate over 32 weeks corrected gestational age 60 micrograms/kg/hour by continuous intravenous infusion adjusted according to response; max. treatment duration 4 days

Child 1–6 months 60 micrograms/kg/hour by continuous intravenous infusion adjusted according to response

Child 6 months–12 years initially 50–200 micrograms/kg by slow intravenous injection over at least 3 minutes followed by 30–120 micrograms/kg/hour by continuous intravenous infusion adjusted according to response

Child 12–18 years initially 30–300 micrograms/kg by slow intravenous injection given in steps of 1–2.5 mg every 2 minutes followed by 30–200 micrograms/kg/hour by continuous intravenous infusion adjusted according to response

Note Initial dose may not be required and lower maintenance doses needed if opioid analgesics also used; reduce dose (or reduce or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia

Status epilepticus section 4.8.2

Administration for administration by mouth, injection solution may be diluted with apple or black currant juice, chocolate sauce, or cola

For continuous intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%

Neonatal intensive care, dilute 15 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 30 micrograms/kg/hour

For rectal administration of the injection solution, attach a plastic applicator onto the end of a syringe; if the volume to be given rectally is too small, dilute with Water for Injections

Midazolam (Non-proprietary) ^(CD3)

Oral liquid, midazolam 2.5 mg/mL, 100 mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 840

Injection, midazolam (as hydrochloride) 1 mg/mL, net price 2-mL amp = 45p, 5-mL amp = 60p, 50-mL vial = £9.56; 2 mg/mL, 5-mL amp = 65p; 5 mg/mL, 2-mL amp = 63p, 10-mL amp = £2.50

Hypnovel[®] (Roche) ^(CD3)

Injection, midazolam (as hydrochloride) 5 mg/mL, 2-mL amp = 71p

■ **Buccal preparation**

Section 4.8.2

TEMAZEPAM

Cautions see notes above and Diazepam, section 4.8.2; **interactions:** Appendix 1 (anxiolytics and hypnotics)

Contra-indications see Diazepam, section 4.8.2

Hepatic impairment see Benzodiazepines, section 4.8.1

Renal impairment see Benzodiazepines, section 4.8.1

Pregnancy see Benzodiazepines, section 4.8.1

Breast-feeding see Benzodiazepines, section 4.8.1

Side-effects see notes above and Diazepam, section 4.8.2

Licensed use tablets not licensed for use in children

Indications and dose

Premedication

- By mouth

Child 12–18 years 10–20 mg 1 hour before procedure

Temazepam (Non-proprietary) ^(CD3)

Tablets, temazepam 10 mg, net price 28-tab pack = £20.55; 20 mg, 28-tab pack = £19.64. Label: 19

Dental prescribing on NHS Temazepam Tablets may be prescribed

Oral solution, temazepam 10 mg/5 mL, net price 300 mL = £55.93. Label: 19

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Temazepam Oral Solution may be prescribed

Note See p. 8 for prescribing requirements of controlled drugs

Ketorolac (Non-proprietary) PoM

Injection, ketorolac trometamol 30 mg/mL, net price 1-mL amp = £1.09

Toradol[®] (Roche) PoM

Injection, ketorolac trometamol 30 mg/mL, net price 1-mL amp = £1.07

15.1.4.2 Non-opioid analgesics

Since non-steroidal anti-inflammatory drugs (NSAIDs) do not depress respiration, do not impair gastro-intestinal motility, and do not cause dependence, they may be useful alternatives or adjuncts to opioids for the relief of postoperative pain. NSAIDs may be inadequate for the relief of severe pain.

Diclofenac, **ibuprofen** (section 10.1.1), **paracetamol** (section 4.7.1), and **ketorolac** are used to relieve post-operative pain in children; diclofenac and paracetamol can be given parenterally and rectally as well as by mouth. Ketorolac is given by intravenous injection.

KETOROLAC TROMETAMOL

Cautions section 10.1.1; **interactions:** Appendix 1 (NSAIDs)

Contra-indications section 10.1.1; also complete or partial syndrome of nasal polyps; haemorrhagic diatheses (including coagulation disorders) and following operations with high risk of haemorrhage or incomplete haemostasis; confirmed or suspected cerebrovascular bleeding; hypovolaemia or dehydration

Hepatic impairment section 10.1.1

Renal impairment max. 60 mg daily by intravenous injection; avoid if serum creatinine greater than 160 micromol/litre; see also section 10.1.1

Pregnancy section 10.1.1

Breast-feeding amount too small to be harmful

Side-effects section 10.1.1; also gastro-intestinal disturbances, taste disturbances, dry mouth; flushing, bradycardia, palpitation, chest pain, hypertension, pallor; dyspnoea, asthma; malaise, euphoria, psychosis, paraesthesia, convulsions, abnormal dreams, hyperkinesia, confusion, hallucinations, urinary frequency, thirst, sweating; hyponatraemia, hyperkalaemia, myalgia; visual disturbances (including optic neuritis); purpura, pain at injection site

Licensed use not licensed for use in children under 16 years

Indications and dose

Short-term management of moderate to severe acute postoperative pain only

- By intravenous injection over at least 15 seconds
Child 6 months–16 years initially 0.5–1 mg/kg (max. 15 mg), then 500 micrograms/kg (max. 15 mg) every 6 hours as required; max. 60 mg daily; max. duration of treatment 2 days
- By intravenous injection over at least 15 seconds
Child 16–18 years initially 10 mg, then 10–30 mg every 4–6 hours as required (up to every 2 hours during initial postoperative period); max. 90 mg daily (children weighing less than 50 kg max. 60 mg daily); max. duration of treatment 2 days

15.1.4.3 Opioid analgesics

Opioid analgesics are now rarely used as premedicants; they are more likely to be administered at induction. Pre-operative use of opioid analgesics is generally limited to children who require control of existing pain. The main side-effects of opioid analgesics are respiratory depression, cardiovascular depression, nausea, and vomiting; for general notes on opioid analgesics and their use in postoperative pain, see section 4.7.2.

For the management of opioid-induced respiratory depression, see section 15.1.7.

Intra-operative analgesia Opioid analgesics given in small doses before or with induction reduce the dose requirement of some drugs used during anaesthesia.

Alfentanil, **fentanyl**, and **remifentanyl** are particularly useful because they act within 1–2 minutes and have short durations of action. The initial doses of alfentanil or fentanyl are followed either by successive intravenous injections or by an intravenous infusion; prolonged infusions increase the duration of effect. Repeated intra-operative doses of alfentanil or fentanyl should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively when monitoring of the child might be less intensive. Alfentanil, fentanyl, and remifentanyl can cause muscle rigidity, particularly of the chest wall muscle or jaw muscle, which can be managed by the use of neuromuscular blocking drugs.

In contrast to other opioids which are metabolised in the liver, remifentanyl undergoes rapid metabolism by non-specific blood and tissue esterases; its short duration of action allows prolonged administration at high dosage, without accumulation, and with little risk of residual postoperative respiratory depression. Remifentanyl should not be given by intravenous injection intra-operatively, but it is well suited to continuous infusion; a supplementary analgesic is given before stopping the infusion of remifentanyl.

ALFENTANIL

Cautions section 4.7.2 and notes above

Contra-indications section 4.7.2

Hepatic impairment section 4.7.2

Renal impairment section 4.7.2

Pregnancy section 4.7.2

Breast-feeding present in milk—withhold breast-feeding for 24 hours

Side-effects section 4.7.2 and notes above; also hypertension, myoclonic movements; *less commonly* arrhythmias, hiccup, laryngospasm; *rarely* epistaxis; also reported cardiac arrest, cough, convulsions, and pyrexia

Indications and dose

To avoid excessive dosage in obese children, dose may need to be calculated on the basis of ideal weight for height

Assisted ventilation: analgesia and enhancement of anaesthesia at induction and during short procedures

- By intravenous injection over 30 seconds

Neonate initially 5–20 micrograms/kg; supplemental doses up to 10 micrograms/kg

Child 1 month–18 years initially 10–20 micrograms/kg; supplemental doses up to 10 micrograms/kg

Assisted ventilation: maintenance of analgesia and enhancement of anaesthesia during longer surgical procedures

- By intravenous infusion

Neonate initially 10–50 micrograms/kg over 10 minutes followed by 30–60 micrograms/kg/hour

Child 1 month–18 years initially 50–100 micrograms/kg over 10 minutes followed by 30–120 micrograms/kg/hour; usual dose with intravenous anaesthetic, 60 micrograms/kg/hour

Note Half-life is prolonged in neonates and accumulation is likely with prolonged use. Clearance may be increased in children 1 month–12 years and higher infusion doses might be needed

Administration for continuous or intermittent intravenous infusion dilute in Glucose 5% or Sodium Chloride 0.9%

Alfentanil (Non-proprietary) CD2

Injection, alfentanil (as hydrochloride) 500 micrograms/mL, net price 2-mL amp = 70p, 10-mL amp = £3.20

Injection, alfentanil (as hydrochloride) 5 mg/mL, net price 1-mL amp = £2.50

Note To be diluted before use

Rapifen® (Janssen) CD2

Injection, alfentanil (as hydrochloride) 500 micrograms/mL, net price 2-mL amp = 63p; 10-mL amp = £2.90

FENTANYL

Cautions see Fentanyl, section 4.7.2 and notes above

Contra-indications see notes in section 4.7.2

Hepatic impairment see notes in section 4.7.2

Renal impairment see notes in section 4.7.2

Pregnancy see notes in section 4.7.2

Breast-feeding see Fentanyl, section 4.7.2

Side-effects see Fentanyl, section 4.7.2 and notes above; also myoclonic movements; *less commonly* laryngospasm; *rarely* asystole, insomnia

Licensed use not licensed for use in children under 2 years; infusion not licensed for use in children under 12 years

Indications and dose

To avoid excessive dosage in obese children, dose may need to be calculated on the basis of ideal weight for height

Spontaneous respiration: analgesia and enhancement of anaesthesia during operation

- By intravenous injection over at least 30 seconds

Child 1 month–12 years initially 1–3 micrograms/kg, then 1 microgram/kg as required

Child 12–18 years initially 50–100 micrograms (max. 200 micrograms on specialist advice), then 25–50 micrograms as required

Assisted ventilation: analgesia and enhancement of anaesthesia during operation

- By intravenous injection over at least 30 seconds

Neonate initially 1–5 micrograms/kg, then 1–3 micrograms/kg as required

Child 1 month–12 years initially 1–5 micrograms/kg, then 1–3 micrograms/kg as required

Child 12–18 years initially 1–5 micrograms/kg, then 50–200 micrograms as required

Assisted ventilation: analgesia and respiratory depression in intensive care

- By intravenous administration

Neonate initially by intravenous injection 1–5 micrograms/kg, then by intravenous infusion, 1.5 micrograms/kg/hour adjusted according to response

Child 1 month–18 years initially by intravenous injection 1–5 micrograms/kg, then by intravenous infusion, 1–6 micrograms/kg/hour adjusted according to response

Analgesia in other situations section 4.7.2

Administration for intravenous infusion, injection solution may be diluted in Glucose 5% or Sodium Chloride 0.9%

Fentanyl (Non-proprietary) CD2

Injection, fentanyl (as citrate) 50 micrograms/mL, net price 2-mL amp = 30p, 10-mL amp = 75p

Sublimaze® (Janssen) CD2

Injection, fentanyl (as citrate) 50 micrograms/mL, net price 10-mL amp = £1.31

REMIFENTANYL

Cautions section 4.7.2 and notes above

Contra-indications section 4.7.2 and notes above; analgesia in conscious patients

Hepatic impairment section 4.7.2

Pregnancy no information available; see also section 4.7.2

Breast-feeding avoid breast-feeding for 24 hours after administration—present in milk in animal studies

Side-effects section 4.7.2 and notes above; also hypertension; *less commonly* hypoxia; *rarely* asystole; AV block and convulsions also reported

Licensed use not licensed for use in children under 1 year

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Analgesia and enhancement of anaesthesia at induction

- By intravenous infusion

Child 12–18 years 30–60 micrograms/kg/hour, with or without an initial dose by intravenous injection of 0.25–1 micrograms/kg over at least 30 seconds

Note If child is to be intubated more than 8 minutes after start of neuromuscular infusion, initial intravenous injection dose is not necessary

Assisted ventilation: analgesia and enhancement of anaesthesia during maintenance of anaesthesia

- By intravenous administration

Neonate by intravenous infusion 24–60 micrograms/kg/hour; additional doses of 1 microgram/kg can be given by intravenous injection during the intravenous infusion

Child 1 month–12 years initially by intravenous injection 0.1–1 micrograms/kg over at least 30 seconds (omitted if not required) then by intravenous infusion 3–78 micrograms/kg/hour according to anaesthetic technique and adjusted according to response; additional doses can be given by intravenous injection during the intravenous infusion

Child 12–18 years initially by intravenous injection 0.1–1 micrograms/kg over at least 30 seconds (omitted if not required) then by intravenous infusion 3–120 micrograms/kg/hour according to anaesthetic technique and adjusted according to response; additional doses can be given by intravenous injection during the intravenous infusion

Spontaneous respiration: analgesia and enhancement of anaesthesia during maintenance of anaesthesia

- By intravenous infusion

Child 12–18 years initially 2.4 micrograms/kg/hour adjusted according to response, usual range 1.5–6 micrograms/kg/hour

Administration for intravenous injection, reconstitute to a concentration of 1 mg/mL; for continuous intravenous infusion, dilute further with Glucose 5% or Sodium Chloride 0.9% to a concentration of 20–25 micrograms/mL for **Child 1–12 years** or 20–250 micrograms/mL (usually 50 micrograms/mL) for **Child 12–18 years**

Remifentanyl (Non-proprietary) ^(C02)

Injection, powder for reconstitution, remifentanyl (as hydrochloride), net price 1-mg vial = £4.61; 2-mg vial = £5.72; 5-mg vial = £23.02

Ultiva® (GSK) ^(C02)

Injection, powder for reconstitution, remifentanyl (as hydrochloride), net price 1-mg vial = £5.12; 2-mg vial = £10.23; 5-mg vial = £25.58

15.1.5 Neuromuscular blocking drugs**Important**

The drugs in this section should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

Neuromuscular blocking drugs used in anaesthesia are also known as **muscle relaxants**. By specific blockade of the neuromuscular junction they enable light anaesthesia to be used with adequate relaxation of the muscles of the abdomen and diaphragm. They also relax the vocal cords and allow the passage of a tracheal tube. Their action differs from the muscle relaxants used in musculoskeletal disorders (section 10.2.2) that act on the spinal cord or brain.

Children who have received a neuromuscular blocking drug should **always** have their respiration assisted or controlled until the drug has been inactivated or antagonised (section 15.1.6). They should also receive sufficient concomitant inhalational or intravenous anaesthetic or sedative drugs to prevent awareness.

Non-depolarising neuromuscular blocking drugs

Non-depolarising neuromuscular blocking drugs (also known as competitive muscle relaxants) compete with acetylcholine for receptor sites at the neuromuscular junction and their action can be reversed with anticholinesterases, such as neostigmine (section 15.1.6). Non-depolarising neuromuscular blocking drugs can be divided into the **aminosteroid** group, comprising pancuronium, rocuronium, and vecuronium, and the **benzylisoquinolinium** group, which includes atracurium, cisatracurium, and mivacurium.

Non-depolarising neuromuscular blocking drugs have a slower onset of action than suxamethonium. These drugs can be classified by their duration of action as short-acting (15–30 minutes), intermediate-acting (30–40 minutes), and long-acting (60–120 minutes), although duration of action is dose-dependent. Drugs with a shorter or intermediate duration of action, such as atracurium and vecuronium, are more widely used than those with a longer duration of action, such as pancuronium.

Non-depolarising neuromuscular blocking drugs have no sedative or analgesic effects and are not considered to trigger malignant hyperthermia.

For children receiving intensive care and who require tracheal intubation and mechanical ventilation, a non-depolarising neuromuscular blocking drug is chosen according to its onset of effect, duration of action, and side-effects. Rocuronium, with a rapid onset of effect, may facilitate intubation. Atracurium or cisatracurium may be suitable for long-term neuromuscular blockade since their duration of action is not dependent on elimination by the liver or the kidneys.

Cautions Allergic cross-reactivity between neuromuscular blocking drugs has been reported; caution is advised in cases of hypersensitivity to these drugs. Their activity is prolonged in children with myasthenia gravis and in hypothermia, therefore lower doses are required.

15.1.4.4 Other drugs for sedation

This section is not included in *BNF for Children*.

Non-depolarising neuromuscular blocking drugs should be used with great care in those with other neuromuscular disorders and those with fluid and electrolyte disturbances, as response in these children is unpredictable. Resistance may develop in children with burns who may require increased doses; low plasma cholinesterase activity in these children requires dose titration for mivacurium. The rate of administration of neuromuscular blocking drugs should be reduced in children with cardiovascular disease. **Interactions:** Appendix 1 (muscle relaxants).

Pregnancy Non-depolarising neuromuscular blocking drugs are highly ionised at physiological pH and are therefore unlikely to cross the placenta in significant amounts.

Breast-feeding Because they are ionised at physiological pH, non-depolarising neuromuscular blocking drugs are unlikely to be present in milk in significant amounts. Breast-feeding may be resumed once the mother has recovered from neuromuscular block.

Side-effects Benzyliisoquinolinium non-depolarising neuromuscular blocking drugs (except cisatracurium) are associated with histamine release, which can cause skin flushing, hypotension, tachycardia, bronchospasm, and very rarely, anaphylactoid reactions. Most aminosteroid neuromuscular blocking drugs produce minimal histamine release. Drugs with vagolytic activity can counteract any bradycardia that occurs during surgery. Acute myopathy has also been reported after prolonged use in intensive care.

Atracurium, a mixture of 10 isomers, is a benzyliisoquinolinium neuromuscular blocking drug with an intermediate duration of action. It undergoes non-enzymatic metabolism which is independent of liver and kidney function, thus allowing its use in children with hepatic or renal impairment. Cardiovascular effects are associated with significant histamine release; histamine release can be minimised by administering slowly or in divided doses over at least 1 minute. Neonates may be more sensitive to the effects of atracurium and lower doses may be required.

Cisatracurium is a single isomer of atracurium. It is more potent and has a slightly longer duration of action than atracurium and provides greater cardiovascular stability because cisatracurium lacks histamine-releasing effects. In children aged 1 month to 12 years, cisatracurium has a shorter duration of action and produces faster spontaneous recovery.

Mivacurium, a benzyliisoquinolinium neuromuscular blocking drug, has a short duration of action. It is metabolised by plasma cholinesterase and muscle paralysis is prolonged in individuals deficient in this enzyme. It is not associated with vagolytic activity or ganglionic blockade although histamine release can occur, particularly with rapid injection. In children under 12 years mivacurium has a faster onset, shorter duration of action, and produces more rapid spontaneous recovery.

Pancuronium, an aminosteroid neuromuscular blocking drug, has a long duration of action and is often used in children receiving long-term mechanical ventilation in intensive care units. It lacks a histamine-releasing effect, but vagolytic and sympathomimetic effects can cause tachycardia and hypertension. The half-life of pancuronium is prolonged in neonates; neonates should

receive postoperative intermittent positive pressure ventilation.

Rocuronium exerts an effect within 2 minutes and has the most rapid onset of any of the non-depolarising neuromuscular blocking drugs. It is an aminosteroid neuromuscular blocking drug with an intermediate duration of action. It is reported to have minimal cardiovascular effects; high doses produce mild vagolytic activity. In most children, the duration of action of rocuronium may be shorter than in adults; however, in neonates and children under 2 years, usual doses may produce a more prolonged action.

Vecuronium, an aminosteroid neuromuscular blocking drug, has an intermediate duration of action. It does not generally produce histamine release and lacks cardiovascular effects. In most children, the duration of action of vecuronium may be shorter than in adults; however, in neonates and children under 2 years, usual doses may produce a more prolonged action.

ATRACURIUM BESILATE

(Atracurium besylate)

Cautions see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; seizures also reported

Licensed use not licensed for use in neonates

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Neuromuscular blockade (short to intermediate duration) for surgery

• By intravenous administration

Neonate initially by *intravenous injection* 300–500 micrograms/kg followed *either* by *intravenous injection*, 100–200 micrograms/kg repeated as necessary *or* by *intravenous infusion*, 300–400 micrograms/kg/hour adjusted according to response

Child 1 month–18 years initially by *intravenous injection* 300–600 micrograms/kg then 100–200 micrograms/kg repeated as necessary *or* initially by *intravenous injection* 300–600 micrograms/kg followed by *intravenous infusion*, 300–600 micrograms/kg/hour adjusted according to response

Neuromuscular blockade during intensive care

• By intravenous administration

Neonate initially by *intravenous injection* 300–500 micrograms/kg followed *either* by *intravenous injection*, 100–200 micrograms/kg repeated as necessary *or* by *intravenous infusion*, 300–400 micrograms/kg/hour adjusted according to response; higher doses may be necessary

Child 1 month–18 years initially by *intravenous injection* 300–600 micrograms/kg (optional) then by *intravenous infusion*, 270–1770 micrograms/kg/hour (usual dose 650–780 micrograms/kg/hour)

Administration for continuous intravenous infusion, dilute to a concentration of 0.5–5 mg/mL with Glucose 5% or Sodium Chloride 0.9%; stability varies with diluent.

Neonatal intensive care, dilute 60 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; minimum concentration of 500 micrograms/mL, max. concentration of 5 mg/mL; an intravenous infusion rate of 0.1 mL/hour provides a dose of 120 micrograms/kg/hour

Atracurium (Non-proprietary) (PoM)

Injection, atracurium besilate 10 mg/mL, net price 2.5-mL amp = £1.70; 5-mL amp = £3.00; 25-mL vial = £14.45

Tracrium® (GSK) (PoM)

Injection, atracurium besilate 10 mg/mL, net price 2.5-mL amp = £1.66; 5-mL amp = £3.00; 25-mL vial = £12.91

CISATRACURIUM

Cautions see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also bradycardia

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Neuromuscular blockade (intermediate duration) during surgery

• By intravenous injection

Child 1 month–2 years initially 150 micrograms/kg, then 30 micrograms/kg repeated approx. every 20 minutes as necessary

Child 2–12 years initially 150 micrograms/kg (80–100 micrograms/kg if not for intubation), then 20 micrograms/kg repeated approx. every 10 minutes as necessary

Child 12–18 years initially 150 micrograms/kg, then 30 micrograms/kg repeated approx. every 20 minutes as necessary

• By intravenous administration

Child 2–18 years initially 150 micrograms/kg by intravenous injection, then by intravenous infusion 180 micrograms/kg/hour, reduced to 60–120 micrograms/kg/hour according to response

Administration for continuous intravenous infusion, dilute to a concentration of 0.1–2 mg/mL with Glucose 5% or Sodium Chloride 0.9%; solutions of 2 mg/mL and 5 mg/mL may be infused undiluted

Cisatracurium (Non-proprietary) (PoM)

Injection, cisatracurium (as besilate) 2 mg/mL, net price 10-mL vial = £7.55; 5 mg/mL, 30-mL vial = £31.09

Nimbex® (GSK) (PoM)

Injection, cisatracurium (as besilate) 2 mg/mL, net price 10-mL amp = £7.55

Forté injection, cisatracurium (as besilate) 5 mg/mL, net price 30-mL vial = £31.09

MIVACURIUM

Cautions see notes above; low plasma cholinesterase activity

Hepatic impairment reduce dose in severe impairment

Renal impairment clinical effect prolonged in renal failure—reduce dose according to response

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Neuromuscular blockade (short duration) during surgery

• By intravenous administration

Child 2–6 months by intravenous injection initially 150 micrograms/kg, then either by intravenous injection 100 micrograms/kg repeated every 6–9 minutes as necessary or by intravenous infusion, 8–10 micrograms/kg/minute, adjusted if necessary every 3 minutes by 1 microgram/kg/minute to usual dose 11–14 micrograms/kg/minute

Child 6 months–12 years by intravenous injection initially 200 micrograms/kg, then either by intravenous injection 100 micrograms/kg repeated every 6–9 minutes as necessary or by intravenous infusion, 8–10 micrograms/kg/minute, adjusted if necessary every 3 minutes by 1 microgram/kg/minute to usual dose 11–14 micrograms/kg/minute

Child 12–18 years by intravenous injection initially 70–250 micrograms/kg, then either by intravenous injection 100 micrograms/kg repeated every 15 minutes as necessary or by intravenous infusion, 8–10 micrograms/kg/minute, adjusted if necessary every 3 minutes by 1 microgram/kg/minute to usual dose of 6–7 micrograms/kg/minute

Administration for intravenous injection, give undiluted or dilute in Glucose 5% or Sodium Chloride 0.9%. Doses up to 150 micrograms/kg may be given over 5–15 seconds, higher doses should be given over 30 seconds. In asthma, cardiovascular disease or in those sensitive to reduced arterial blood pressure, give over 60 seconds.

Mivacron® (GSK) (PoM)

Injection, mivacurium (as chloride) 2 mg/mL, net price 5-mL amp = £2.79; 10-mL amp = £4.51

PANCURONIUM BROMIDE

Cautions see notes above

Hepatic impairment possibly slower onset, higher dose requirement, and prolonged recovery time

Renal impairment use with caution; prolonged duration of block

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Neuromuscular blockade (long duration) during surgery

- By intravenous injection

Neonate initially 100 micrograms/kg, then 50 micrograms/kg repeated as necessary

Child 1 month–18 years initially 100 micrograms/kg, then 20 micrograms/kg repeated as necessary

Administration for intravenous injection, give undiluted or dilute in Glucose 5% or Sodium Chloride 0.9%

Pancuronium (Non-proprietary) (PoM)

Injection, pancuronium bromide 2 mg/mL, net price 2-mL amp = £4.00

ROCURONIUM BROMIDE

Cautions see notes above

Hepatic impairment reduce dose

Renal impairment reduce maintenance dose; prolonged paralysis

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use not licensed for use in children for assisted ventilation in intensive care

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Neuromuscular blockade (intermediate duration) during surgery

- By intravenous administration

Neonate initially by intravenous injection 600 micrograms/kg, then either by intravenous injection, 150 micrograms/kg repeated as required or by intravenous infusion, 300–600 micrograms/kg/hour adjusted according to response

Child 1 month–18 years initially by intravenous injection 600 micrograms/kg, then either by intravenous injection, 150 micrograms/kg repeated as required or by intravenous infusion, 300–600 micrograms/kg/hour adjusted according to response

Assisted ventilation in intensive care

- By intravenous administration

Child 1 month–18 years initially by intravenous injection 600 micrograms/kg (optional), then by intravenous infusion, 300–600 micrograms/kg/hour for first hour, then adjusted according to response

Administration for continuous intravenous infusion or via drip tubing, may be diluted with Glucose 5% or Sodium Chloride 0.9%

Rocuronium (Non-proprietary) (PoM)

Injection, rocuronium bromide 10 mg/mL, net price 5-mL vial = £3.00, 10-mL vial = £6.00

Esmeron® (MSD) (PoM)

Injection, rocuronium bromide 10 mg/mL, net price 5-mL vial = £2.89, 10-mL vial = £5.79

VECURONIUM BROMIDE

Cautions see notes above

Hepatic impairment caution in significant impairment

Renal impairment caution in renal failure

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Licensed use not licensed for assisted ventilation in intensive care

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Neuromuscular blockade (intermediate duration) during surgery

- By intravenous administration

Neonate by intravenous injection initially 80 micrograms/kg, then 30–50 micrograms/kg adjusted according to response

Child 1 month–18 years by intravenous injection initially 80–100 micrograms/kg, then either by intravenous injection, 20–30 micrograms/kg repeated as required or by intravenous infusion, 0.8–1.4 micrograms/kg/minute, adjusted according to response

Assisted ventilation in intensive care

- By intravenous injection

Neonate initially 80 micrograms/kg, then 30–50 micrograms/kg adjusted according to response

- By intravenous administration

Neonate by intravenous injection 80 micrograms/kg, then by intravenous infusion, 0.8–1.4 micrograms/kg/minute, adjusted according to response (risk of accumulation—consider interruption of infusion)

Child 1 month–18 years initially by intravenous injection 80–100 micrograms/kg (optional), then by intravenous infusion 0.8–1.4 micrograms/kg/minute, adjusted according to response; up to 3 micrograms/kg/minute may be required

Administration reconstitute each vial with 5 mL Water for Injections to give 2 mg/mL solution; alternatively reconstitute with up to 10 mL Glucose 5% or Sodium Chloride 0.9% or Water for Injections—unsuitable for further dilution if not reconstituted with Water for Injections.

For continuous intravenous infusion, dilute reconstituted solution to a concentration up to 40 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; reconstituted solution can also be given via drip tubing.

Neonatal intensive care, reconstitute each vial with 5 mL Water for Injections to give a 2 mg/mL solution. Dilute 5 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.5 mL/hour provides a dose of 50 micrograms/kg/hour; minimum concentration of 40 micrograms/mL.

Norcuron® (MSD) (PoM)

Injection, powder for reconstitution, vecuronium bromide, net price 10-mg vial = £3.37 (with water for injections)

Depolarising neuromuscular blocking drugs

Suxamethonium has the most rapid onset of action of any of the neuromuscular blocking drugs and is ideal if fast onset and brief duration of action are required e.g. with tracheal intubation. Neonates and young children are less sensitive to suxamethonium and a higher dose may be required.

Suxamethonium acts by mimicking acetylcholine at the neuromuscular junction but hydrolysis is much slower than for acetylcholine; depolarisation is therefore prolonged, resulting in neuromuscular blockade. Unlike the non-depolarising neuromuscular blocking drugs, its action cannot be reversed and recovery is spontaneous; anticholinesterases such as neostigmine potentiate the neuromuscular block.

Suxamethonium should be given after anaesthetic induction because paralysis is usually preceded by painful muscle fasciculations. Bradycardia may occur; premedication with atropine (section 15.1.3) reduces bradycardia as well as the excessive salivation associated with suxamethonium use.

Prolonged paralysis may occur in **dual block**, which occurs with high or repeated doses of suxamethonium and is caused by the development of a non-depolarising block following the initial depolarising block; edrophonium (section 15.1.6) may be used to confirm the diagnosis of dual block. Children with myasthenia gravis are resistant to suxamethonium but can develop dual block resulting in delayed recovery. Prolonged paralysis may also occur in those with low or atypical plasma cholinesterase. Assisted ventilation should be continued until muscle function is restored.

SUXAMETHONIUM CHLORIDE (Succinylcholine chloride)

Cautions see notes above; hypersensitivity to other neuromuscular blocking drugs; patients with cardiac, respiratory or neuromuscular disease; raised intra-ocular pressure (avoid in penetrating eye injury); severe sepsis (risk of hyperkalaemia); **interactions:** Appendix 1 (muscle relaxants)

Contra-indications family history of malignant hyperthermia, hyperkalaemia; major trauma, severe burns, neurological disease involving acute wasting of major muscle, prolonged immobilisation—risk of hyperkalaemia; personal or family history of congenital myotonic disease, Duchenne muscular dystrophy; low plasma-cholinesterase activity (including severe liver disease, see below)

Hepatic impairment prolonged apnoea may occur in severe liver disease because of reduced hepatic synthesis of pseudocholinesterase

Pregnancy mildly prolonged neuromuscular blockade may occur

Breast-feeding unlikely to be present in breast milk in significant amounts (ionised at physiological pH); breast-feeding may be resumed once the mother recovered from neuromuscular block

Side-effects see notes above; also increased gastric pressure; hyperkalaemia; postoperative muscle pain, myoglobinuria, myoglobinaemia; increased intra-ocular pressure; flushing, rash; *rarely* arrhythmias, cardiac arrest; bronchospasm, apnoea, prolonged respiratory depression; limited jaw mobility; *very rarely* anaphylactic reactions, malignant hyperthermia; *also reported* hypertension, hypotension, rhabdomyolysis

Indications and dose

Neuromuscular blockade (short duration) during surgery

• By intravenous injection

Neonate 2 mg/kg produces 5–10 minutes neuromuscular blockade

Child 1 month–1 year 2 mg/kg

Child 1–18 years 1 mg/kg

• By intramuscular injection (onset in 2–3 minutes)

Neonate up to 4 mg/kg produces 10–30 minutes neuromuscular blockade

Child 1 month–1 year up to 4–5 mg/kg

Child 1–12 years up to 4 mg/kg; max. 150 mg

Administration for *intravenous injection*, give undiluted or dilute with Glucose 5% or Sodium Chloride 0.9%

Suxamethonium Chloride (Non-proprietary) (PoM)

Injection, suxamethonium chloride 50 mg/mL, net price 2-mL amp = 58p, 2-mL prefilled syringe = £8.45

Anectine® (GSK) (PoM)

Injection, suxamethonium chloride 50 mg/mL, net price 2-mL amp = 71p

15.1.6 Drugs for reversal of neuromuscular blockade

Important

The drugs in this section should only be administered by, or under the direct supervision of, personnel experienced in their use.

Anticholinesterases

Anticholinesterases reverse the effects of the non-depolarising (competitive) neuromuscular blocking drugs such as pancuronium, but they prolong the action of the depolarising neuromuscular blocking drug suxamethonium.

Edrophonium has a transient action and may be used in the diagnosis of suspected dual block due to suxamethonium. Atropine (section 15.1.3) is given before or with edrophonium to prevent muscarinic effects of edrophonium; it is also used in the diagnosis of myasthenia gravis (section 10.2.1).

Neostigmine has a longer duration of action than edrophonium and is used specifically for reversal of non-depolarising (competitive) blockade. It acts within one minute of intravenous injection and its effects last for 20 to 30 minutes; a second dose may then be necessary. Glycopyrronium or alternatively atropine (section 15.1.3), given before or with neostigmine, prevent bradycardia, excessive salivation, and other muscarinic effects of neostigmine.

EDROPHONIUM CHLORIDE

Cautions section 10.2.1; atropine should also be given

Contra-indications section 10.2.1

Pregnancy section 10.2.1

Breast-feeding section 10.2.1

Side-effects section 10.2.1

Indications and dose

Brief reversal of non-depolarising neuromuscular blockade

- By intravenous injection over several minutes

Child 1 month–18 years 500–700 micrograms/kg (after or with atropine)

Myasthenia gravis section 10.2.1

Edrophonium (Non-proprietary) (PoM)

Injection, edrophonium chloride 10 mg/mL, net price 1-mL amp = £19.50

NEOSTIGMINE METILSULFATE

(Neostigmine methylsulfate)

Cautions section 10.2.1; glycopyrronium or atropine should also be given

Contra-indications section 10.2.1

Renal impairment section 10.2.1

Pregnancy section 10.2.1

Breast-feeding section 10.2.1

Side-effects section 10.2.1

Indications and dose

Reversal of non-depolarising muscle block

- By intravenous injection over 1 minute

Neonate 50 micrograms/kg, after or with glycopyrronium or atropine; a further dose of 25 micrograms/kg may be required

Child 1 month–12 years 50 micrograms/kg (max. 2.5 mg) after or with glycopyrronium or atropine; a further dose of 25 micrograms/kg may be required

Child 12–18 years 50 micrograms/kg (max. 2.5 mg) after or with glycopyrronium or atropine; a further dose of 25 micrograms/kg (max. 2.5 mg) may be required

Myasthenia gravis section 10.2.1

Administration for intravenous injection, give undiluted or dilute with Glucose 5% or Sodium Chloride 0.9%

Neostigmine (Non-proprietary) (PoM)

Injection, neostigmine metilsulfate 2.5 mg/mL, net price 1-mL amp = 50p

With glycopyrronium

Glycopyrronium-Neostigmine (Non-proprietary) (PoM)

Injection, neostigmine metilsulfate 2.5 mg, glycopyrronium bromide 500 micrograms/mL, net price 1-mL amp = £1.15

Dose

Reversal of non-depolarising neuromuscular blockade

- By intravenous injection over 10–30 seconds

Child 1 month–18 years 0.02 mL/kg (or 0.2 mL/kg of a 1 in 10 dilution), dose may be repeated if required (total max. 2 mL)

Administration for intravenous injection, may be diluted with Sodium Chloride 0.9%

Other drugs for reversal of neuromuscular blockade

Sugammadex is a modified gamma cyclodextrin that can be used in children for the routine reversal of neuromuscular blockade induced by rocuronium (section 15.1.5).

The *Scottish Medicines Consortium*, p. 3 has advised (February 2013) that sugammadex (*Bridion*®) is accepted for restricted use within NHS Scotland for the routine reversal of neuromuscular blockade in high-risk patients only, or where prompt reversal of neuromuscular block is required.

SUGAMMADEX

Cautions recurrence of neuromuscular blockade—monitor respiratory function until fully recovered; recovery may be delayed in cardiovascular disease; pre-existing coagulation disorders or use of anticoagulants (unrelated to surgery); wait 24 hours before re-administering rocuronium; **interactions:** Appendix 1 (sugammadex)

Renal impairment avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy use with caution—no information available

Side-effects bronchospasm, bradycardia, cardiac arrest, hypersensitivity reactions

Indications and dose

Routine reversal of neuromuscular blockade induced by rocuronium

- By intravenous injection

Child 2–18 years 2 mg/kg (consult product literature)

Administration for intravenous injection dose may be diluted to a concentration of 10 mg/mL with Sodium Chloride 0.9%

Bridion® (MSD) (PoM)

Injection, sugammadex (as sodium salt) 100 mg/mL, net price 2-mL amp = £59.64, 5-mL amp = £149.10

Electrolytes Na⁺ 0.42 mmol/mL

15.1.7 Antagonists for central and respiratory depression

Important

The drugs in this section should only be administered by, or under the direct supervision of, personnel experienced in their use.

Respiratory depression is a major concern with opioid analgesics and it may be treated by artificial ventilation or be reversed by an opioid antagonist. **Naloxone** given intravenously immediately reverses opioid-induced respiratory depression but the dose may have to be repeated because of its **short duration of action**. Intramuscular injection of naloxone produces a more gradual and prolonged effect but absorption may be erratic. Care is required in children requiring pain relief because naloxone also antagonises the analgesic effect of opioids.

Neonates Naloxone is used in newborn infants to reverse respiratory depression and sedation resulting from the use of opioids by the mother, usually for pain during labour. In neonates the effects of opioids may persist for up to 48 hours and in such cases naloxone is often given by intramuscular injection for its prolonged effect. In severe respiratory depression after birth, breathing should first be established (using artificial means if necessary) and naloxone administered only if use of opioids by the mother is thought to cause the respiratory depression; the infant should be monitored closely and further doses of naloxone administered as necessary.

Flumazenil is a benzodiazepine antagonist for the reversal of the central sedative effects of benzodiazepines after anaesthetic and similar procedures. Flumazenil has a shorter half-life and duration of action than diazepam and midazolam, so children may become resedated.

FLUMAZENIL

Cautions short-acting (repeat doses may be necessary—benzodiazepine effects may persist for at least 24 hours); benzodiazepine dependence (may precipitate withdrawal symptoms); prolonged benzodiazepine therapy for epilepsy (risk of convulsions); history of panic disorders (risk of recurrence); ensure neuromuscular blockade cleared before giving; avoid rapid injection in high-risk or anxious children and following major surgery; head injury (rapid reversal of benzodiazepine sedation may cause convulsions)

Contra-indications life-threatening condition (e.g. raised intracranial pressure, status epilepticus) controlled by benzodiazepines

Hepatic impairment carefully titrate dose

Pregnancy not known to be harmful

Breast-feeding avoid breast-feeding for 24 hours

Side-effects nausea and vomiting; *less commonly* palpitation, anxiety, fear; *also reported* transient hypertension, tachycardia, flushing, agitation, convulsions (particularly in those with epilepsy), dizziness, sensory disturbance, chills, sweating

Licensed use not licensed for use in children under 1 year; not licensed for use by intravenous infusion in children; not licensed for use in children in intensive care

Indications and dose

Reversal of sedative effects of benzodiazepines

- By intravenous injection over 15 seconds

Neonate 10 micrograms/kg, repeat at 1-minute intervals if required

Child 1 month–18 years 10 micrograms/kg (max. 200 micrograms), repeated at 1-minute intervals if required; max. total dose of 50 micrograms/kg (1 mg) (2 mg in intensive care)

- By intravenous infusion, if drowsiness recurs after injection

Neonate 2–10 micrograms/kg/hour, adjusted according to response

Child 1 month–18 years 2–10 micrograms/kg/hour, adjusted according to response; max. 400 micrograms/hour

Overdosage with benzodiazepines see Emergency Treatment of Poisoning p. 29

Administration for *continuous intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%

Flumazenil (Non-proprietary) POM

Injection, flumazenil 100 micrograms/mL, net price 5-mL amp = £13.50

NALOXONE HYDROCHLORIDE

Cautions cardiovascular disease or those receiving cardiotoxic drugs (serious adverse cardiovascular effects reported); maternal physical dependence on opioids (may precipitate withdrawal in newborn); pain (see also under Titration of Dose, below); has short duration of action (see notes above)

Titration of dose In postoperative use, the dose should be titrated for each child in order to obtain sufficient respiratory response; however, naloxone antagonises analgesia

Pregnancy use only if potential benefit outweighs risk

Breast-feeding not orally bioavailable

Side-effects nausea, vomiting; hypotension, hypertension, ventricular tachycardia and fibrillation, cardiac arrest; hyperventilation, dyspnoea, pulmonary oedema; headache, dizziness; *less commonly* diarrhoea, dry mouth, agitation, excitement, paraesthesia, tremor, sweating; *very rarely* seizures and erythema multiforme

Indications and dose

Reversal of respiratory and CNS depression in neonate following maternal opioid use during labour

- By intramuscular injection

Neonate 200 micrograms (60 micrograms/kg) as a single dose at birth

- By intravenous or subcutaneous injection

Neonate 10 micrograms/kg, repeated every 2–3 minutes if required

Reversal of postoperative respiratory depression

- By intravenous injection

Neonate 1 microgram/kg, repeated every 2–3 minutes if required

Child 1 month–12 years 1 microgram/kg, repeated every 2–3 minutes if required

Child 12–18 years 1.5–3 micrograms/kg; if response inadequate, give subsequent doses of 100 micrograms every 2 minutes

Overdosage with opioids see Emergency Treatment of Poisoning, p. 27

Preparation

See Emergency Treatment of Poisoning, p. 28

15.1.8 Drugs for malignant hyperthermia

Important

The drugs in this section should only be administered by, or under the direct supervision of, personnel experienced in their use.

Malignant hyperthermia is a rare but potentially lethal complication of anaesthesia. It is characterised by a rapid rise in temperature, increased muscle rigidity, tachycardia, and acidosis. The most common triggers of malignant hyperthermia are the volatile anaesthetics. Suxamethonium has also been implicated, but malignant hyperthermia is more likely if it is given following a volatile anaesthetic. Volatile anaesthetics and suxamethonium should be avoided during anaesthesia in children at high risk of malignant hyperthermia.

Dantrolene is used in the treatment of malignant hyperthermia. It acts on skeletal muscle cells by interfering with calcium efflux, thereby stopping the contractile process.

DANTROLENE SODIUM

Cautions avoid extravasation (risk of tissue necrosis); interactions: Appendix 1 (muscle relaxants)

Pregnancy use only if potential benefit outweighs risk

Breast-feeding present in milk—use only if potential benefit outweighs risk

Side-effects hepatotoxicity, pulmonary oedema, dizziness, weakness, and injection-site reactions including erythema, rash, swelling, and thrombophlebitis

Licensed use not licensed for use in children

Indications and dose

Malignant hyperthermia

- By rapid intravenous injection

Child 1 month–18 years initially 2–3 mg/kg, then 1 mg/kg repeated as required (total max. dose 10 mg/kg)

Chronic severe spasticity of voluntary muscle see section 10.2.2

Dantrium Intravenous[®] (SpePharm) (PoM)

Injection, powder for reconstitution, dantrolene sodium, net price 20-mg vial = £51.00 (hosp. only)

Use of local anaesthetics Local anaesthetic drugs act by causing a reversible block to conduction along nerve fibres. They vary widely in their potency, toxicity, duration of action, stability, solubility in water, and ability to penetrate mucous membranes. These factors determine their application, e.g. topical (surface), infiltration, peripheral nerve block, intravenous regional anaesthesia (Bier's block), plexus, epidural (extradural), or spinal (intrathecal or subarachnoid) block. Local anaesthetics may also be used for postoperative pain relief, thereby reducing the need for analgesics such as opioids.

Administration The dose of local anaesthetic depends on the injection site and the procedure used. In determining the safe dosage, it is important to take account of the rate of absorption and excretion, and of the potency. The child's age, weight, physique, and clinical condition, and the vascularity of the administration site and the duration of administration, must also be considered.

Uptake of local anaesthetics into the systemic circulation determines their duration of action and produces toxicity.

Great care must be taken to avoid accidental intravascular injection; local anaesthetic injections should be given slowly in order to detect inadvertent intravascular administration. When prolonged analgesia is required, a long-acting local anaesthetic is preferred to minimise the likelihood of cumulative systemic toxicity. Local anaesthesia around the oral cavity may impair swallowing and therefore increases the risk of aspiration.

Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so **careful surveillance** for toxic effects (see Toxicity and Side-effects, p. 655) is necessary during the first 30 minutes after injection.

Epidural anaesthesia is combined with general anaesthesia for certain surgical procedures in children.

Use of vasoconstrictors Local anaesthetics cause dilatation of blood vessels. The addition of a vasoconstrictor such as **adrenaline (epinephrine)** to the local anaesthetic preparation diminishes local blood flow, slowing the rate of absorption and thereby prolonging the anaesthetic effect. Great care should be taken to avoid inadvertent intravenous administration of a preparation containing adrenaline, and it is **not** advisable to give adrenaline with a local anaesthetic injection in digits or appendages because of the risk of ischaemic necrosis.

Adrenaline must be used in a low concentration when administered with a local anaesthetic (but see also Dental Anaesthesia, p. 655). The total dose of adrenaline should **not** exceed 5 micrograms/kg (1 mL/kg of a 1 in 200 000 solution) and it is essential not to exceed a concentration of 1 in 200 000 (5 micrograms/mL) if more than 50 mL of the mixture is to be injected. Care must also be taken to calculate a safe maximum dose of local anaesthetic when using combination products. For prescribing information on adrenaline, see section 2.7.2. For drug interactions of adrenaline, see Appendix 1 (sympathomimetics).

In children with severe hypertension or unstable cardiac rhythm, the use of adrenaline with a local anaesthetic may be hazardous. For these children an anaesthetic without adrenaline should be used.

The use of local anaesthetics by injection or by application to mucous membranes to produce local analgesia is discussed in this section.

See also section 1.7 (anus), section 11.7 (eye), section 12.3 (oropharynx), and section 13.3 (skin).

15.2 Local anaesthesia

Important

The drugs in section 15.2 should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

Dental anaesthesia **Lidocaine** is widely used in dental procedures; it is most often used in combination with **adrenaline** (epinephrine). Lidocaine 2% combined with adrenaline 1 in 80 000 (12.5 micrograms/mL) is a safe and effective preparation; there is no justification for using higher concentrations of adrenaline. See also Use of Vasoconstrictors, p. 654.

The local anaesthetics **articaine** and **mepivacaine** are also used in dentistry; they are available in cartridges suitable for dental use. Mepivacaine is available with or without adrenaline, and articaine is available with adrenaline.

In children with severe hypertension or unstable cardiac rhythm, mepivacaine without adrenaline may be used. Alternatively, **prilocaine** with or without felypressin can be used but there is no evidence that it is any safer. Felypressin can cause coronary vasoconstriction when used at high doses; limit dose in children with coronary artery disease.

Cautions of local anaesthetics Local anaesthetics should be administered with caution in children, especially if debilitated (consider dose reduction) or those with impaired cardiac conduction, cardiovascular disease, hypovolaemia, shock, impaired respiratory function, epilepsy, or myasthenia gravis. See also Administration and Use of Vasoconstrictors, above.

Contra-indications of local anaesthetics Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. In such circumstances, increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH. See also Use of Vasoconstrictors, p. 654.

Local anaesthetic preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier's block).

Local anaesthetics can cause ototoxicity and should not be applied to the middle ear. They are also contra-indicated in children with complete heart block.

Toxicity and side-effects A single application of a topical lidocaine preparation does not generally cause systemic side-effects. Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection.

The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems. CNS effects include a feeling of inebriation and lightheadedness followed by drowsiness, numbness of the tongue and perioral region, restlessness, paraesthesia (including sensations of hot and cold), dizziness, blurred vision, tinnitus, headache, nausea and vomiting, muscle twitching, tremors, and convulsions. Transient excitation may also occur, followed by depression with drowsiness, respiratory failure, unconsciousness, and coma. Effects on the cardiovascular system include myocardial depression and peripheral vasodilatation resulting in hypotension and bradycardia; arrhythmias and cardiac arrest can occur.

Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine,

prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

Management of severe local anaesthetic-induced cardiovascular toxicity

After injection of a bolus of local anaesthetic, toxicity may develop at any time in the following hour. In the event of signs of toxicity during injection, the administration of the local anaesthetic must be stopped immediately.

Cardiovascular status must be assessed and cardiopulmonary resuscitation procedures must be followed, see section 2.7.3 (Cardiopulmonary Resuscitation).

In the event of local anaesthetic-induced cardiac arrest, standard cardiopulmonary resuscitation should be initiated immediately. Lidocaine must not be used as anti-arrhythmic therapy.

If the child does not respond rapidly to standard procedures, 20% lipid emulsion such as *Intralipid*® [unlicensed indication] should be given intravenously at an initial bolus dose of 1.5 mL/kg over 1 minute, followed by an infusion of 15 mL/kg/hour. After 5 minutes, if cardiovascular stability has not been restored or circulation deteriorates, give a maximum of two further bolus doses of 1.5 mL/kg over 1 minute, 5 minutes apart, and increase the infusion rate to 30 mL/kg/hour. Continue infusion until cardiovascular stability and adequate circulation are restored or maximum cumulative dose of 12 mL/kg is given.

Standard cardiopulmonary resuscitation must be maintained throughout lipid emulsion treatment.

Propofol is not a suitable alternative to lipid emulsion.

Further advice on ongoing treatment should be obtained from the **National Poisons Information Service**, p. 23.

Detailed treatment algorithms and accompanying notes are available at www.toxbase.org or www.aagbi.org (search site for: local anaesthetic toxicity).

Articaine

Articaine is an amide-type local anaesthetic used for dental anaesthesia (see Dental Anaesthesia, p. 655). It is available in a preparation that also contains adrenaline (see Use of Vasoconstrictors, p. 654).

ARTICAINE HYDROCHLORIDE WITH ADRENALINE

(Carticaine hydrochloride with adrenaline)

Cautions see Cautions of Local Anaesthetics, p. 655 and Adrenaline, section 2.7.2

Contra-indications see Contra-indications of Local Anaesthetics, p. 655 and Adrenaline, section 2.7.2

Hepatic impairment use with caution; increased risk of side-effects in severe impairment

Renal impairment see Adrenaline, section 2.7.2

Pregnancy use only if potential benefit outweighs risk—no information available

Breast-feeding avoid breast-feeding for 48 hours after administration

Side-effects see Toxicity and Side-effects, p. 655 and Adrenaline, section 2.7.2; also methaemoglobinaemia (see Prilocaine (p. 658) for treatment)

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Infiltration anaesthesia in dentistry

Child 4–18 years consult expert dental sources; **important:** see also Administration, p. 654

Septanest® (Septodont) (PoM)

Injection, articaine hydrochloride 40 mg/mL, adrenaline 1 in 200 000 (5 micrograms/mL), net price 2.2-mL cartridge = 41p

Excipients include sulfites

Injection, articaine hydrochloride 40 mg/mL, adrenaline 1 in 100 000 (10 micrograms/mL), net price 2.2-mL cartridge = 41p

Excipients include sulfites

Bupivacaine

Bupivacaine has a longer duration of action than other local anaesthetics. It has a slow onset of action, taking up to 30 minutes for full effect. It is often used in lumbar epidural blockade and is particularly suitable for continuous epidural analgesia in labour, or for postoperative pain relief. It is the principal drug used for spinal anaesthesia. Hyperbaric solutions containing glucose may be used for spinal block.

BUPIVACAINE HYDROCHLORIDE

Cautions see Cautions of Local Anaesthetics, p. 655; myocardial depression may be more severe and more resistant to treatment; cardiovascular disease; hypertension; hypotension; cerebral atheroma; **interactions:** Appendix 1 (bupivacaine)

Contra-indications see Contra-indications of Local Anaesthetics, p. 655

Hepatic impairment use with caution in severe impairment

Renal impairment use with caution in severe impairment

Pregnancy large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block; use lower doses for intrathecal use during late pregnancy

Breast-feeding amount too small to be harmful

Side-effects see Toxicity and Side-effects, p. 655

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Adjusted according to child's physical status and nature of procedure, seek expert advice—**important:** see also under Administration, p. 654

Bupivacaine (Non-proprietary) (PoM)

Injection, anhydrous bupivacaine hydrochloride 2.5 mg/mL (0.25%), net price 10 mL = 88p; 5 mg/mL (0.5%), 10 mL = 92p

Infusion (epidural), anhydrous bupivacaine hydrochloride 1 mg/mL (0.1%), net price 100 mL = £8.41, 250 mL = £10.59; 1.25 mg/mL (0.125%), 250 mL = £10.80

Marcaïn® (AstraZeneca) (PoM)

Injection, anhydrous bupivacaine hydrochloride 2.5 mg/mL (Marcaïn® 0.25%), net price 10-mL *Polyamp*® = £1.06; 5 mg/mL (Marcaïn® 0.5%), 10-mL *Polyamp*® = £1.21

Marcaïn Heavy® (AstraZeneca) (PoM)

Injection, anhydrous bupivacaine hydrochloride 5 mg/mL (0.5%), glucose 80 mg/mL, net price 4-mL amp = £1.45

With adrenaline

For prescribing information on adrenaline, see section 2.7.2; see also Use of Vasoconstrictors, p. 654

Bupivacaine and Adrenaline (Non-proprietary) (PoM)

Injection, anhydrous bupivacaine hydrochloride 2.5 mg/mL (0.25%), adrenaline 1 in 200 000 (5 micrograms/mL), net price 10-mL amp = £1.40

Injection, anhydrous bupivacaine hydrochloride 5 mg/mL (0.5%), adrenaline 1 in 200 000 (5 micrograms/mL), net price 10-mL amp = £2.10

Levobupivacaine

Levobupivacaine, an isomer of bupivacaine, has anaesthetic and analgesic properties similar to bupivacaine but is thought to have fewer adverse effects.

LEVOPRIVACAINE

Note Levobupivacaine is an isomer of bupivacaine

Cautions see Cautions of Local Anaesthetics, p. 655; cardiovascular disease; **interactions:** Appendix 1 (levobupivacaine)

Contra-indications see Contra-indications of Local Anaesthetics, p. 655

Hepatic impairment use with caution

Pregnancy large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block; avoid if possible in first trimester—*toxicity in animal studies*; may cause fetal distress syndrome; do not use for paracervical block in obstetrics; do not use 7.5 mg/mL strength in obstetrics

Breast-feeding amount too small to be harmful

Side-effects see Toxicity and Side-effects, p. 655; also sweating, pyrexia, anaemia

Licensed use not licensed for use in children except for analgesia by ilioinguinal or iliohypogastric block

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Adjusted according to child's physical status and nature of procedure, seek expert advice—**important:** see also under Administration, p. 654

Chirocaine® (AbbVie) (PoM)

Injection, levobupivacaine (as hydrochloride) 2.5 mg/mL, net price 10-mL amp = £1.41; 5 mg/mL, 10-mL amp = £1.62; 7.5 mg/mL, 10-mL amp = £2.42

Note For 1.25 mg/mL concentration dilute standard solutions with sodium chloride 0.9%

Infusion, levobupivacaine (as hydrochloride) 1.25 mg/mL, net price 100 mL = £7.26, 200 mL = £12.20

Lidocaine

Lidocaine is effectively absorbed from mucous membranes and is a useful surface anaesthetic in concentrations up to 10%. Except for surface anaesthesia and dental anaesthesia, solutions should **not** usually exceed 1% in strength. The duration of the block (with adrenaline) is about 90 minutes.

Application of a mixture of lidocaine and prilocalaine (*EMLA*®) under an occlusive dressing provides surface anaesthesia for 1–2 hours. *EMLA*® does not appear to be effective in providing local anaesthesia for heel lancing in neonates.

LIDOCAINE HYDROCHLORIDE (Lignocaine hydrochloride)

Cautions see Cautions of Local Anaesthetics, p. 655 and section 2.3.2; hypertension; topical preparations can damage plastic cuffs of endotracheal tubes

Contra-indications see notes above, Contra-indications of Local Anaesthetics (p. 655), and section 2.3.2

Hepatic impairment section 2.3.2

Renal impairment section 2.3.2

Pregnancy large doses can cause fetal bradycardia; large doses during delivery can cause neonatal respiratory depression, hypotonia, or bradycardia after paracervical or epidural block

Breast-feeding section 2.3.2

Side-effects see Toxicity and Side-effects, p. 655 and section 2.3.2; also methaemoglobinaemia (see Prilocaine (p. 658) for treatment), nystagmus, rash; hypoglycaemia also reported following intrathecal or extradural administration

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Infiltration anaesthesia

• By injection

(see also Administration, p. 654, and *Important* warning below)

Neonate according to nature of procedure, up to 3 mg/kg (0.3 mL/kg of 1% solution), repeated not more often than every 4 hours

Child 1 month–12 years according to nature of procedure, up to 3 mg/kg (0.3 mL/kg of 1% solution), repeated not more often than every 4 hours

Child 12–18 years according to weight of child and nature of procedure, max. 200 mg, repeated not more often than every 4 hours

Surface anaesthesia see preparations below

Ventricular arrhythmias, neonatal seizures section 2.3.2

Intravenous regional anaesthesia and nerve blocks seek expert advice

Dental anaesthesia seek expert advice

Important

The licensed doses stated above may not be appropriate in some settings and expert advice should be sought

▲ Lidocaine hydrochloride injections

Lidocaine (Non-proprietary) (PoM)

Injection, lidocaine hydrochloride 5 mg/mL (0.5%), net price 10-mL amp = 50p; 10 mg/mL (1%), 2-mL amp = 27p, 5-mL amp = 27p, 10-mL amp = 40p, 10-mL prefilled syringe = £8.48, 20-mL amp = 76p; 20 mg/mL (2%), 2-mL amp = 31p, 5-mL amp = 31p

▲ With adrenaline

For prescribing information on adrenaline see section 2.7.2; see also Use of Vasoconstrictors, p. 654.

Xylocaine® (AstraZeneca) (PoM)

Injection, anhydrous lidocaine hydrochloride 10 mg/mL (1%), adrenaline 1 in 200 000 (5 micrograms/mL), net price 20-mL vial = £1.93

Excipients include sulfites

Injection, anhydrous lidocaine hydrochloride 20 mg/mL (2%), adrenaline 1 in 200 000 (5 micrograms/mL), net price 20-mL vial = £1.77

Excipients include sulfites

▲ Lidocaine injections for dental use

A variety of lidocaine injections with adrenaline are available in dental cartridges; brand names include *Lignospan Special*®, *Rexocaine*®, and *Xylocaine*®.

For prescribing information on adrenaline see section 2.7.2; see also Use of Vasoconstrictors, p. 654.

Note Consult expert dental sources for specific advice in relation to dose of lidocaine for dental anaesthesia

▲ Lidocaine for surface anaesthesia

Lidocaine (Non-proprietary)

Ointment, lidocaine 5%, net price 15 g = £6.18

Dose

Dental practice

Child rub gently into dry gum

Pain relief (in anal fissures, haemorrhoids, pruritus ani, pruritus vulvae, herpes zoster, or herpes labialis), lubricant in cystoscopy or proctoscopy

Child apply 1–2 mL when necessary; avoid long-term use

Instillagel® (CliniMed)

Gel, lidocaine hydrochloride 2%, chlorhexidine gluconate solution 0.25%, in a sterile lubricant basis in disposable syringe, net price 6-mL syringe = 23p, 11-mL syringe = 14p

Excipients include hydroxybenzoates (parabens)

Laryngojet® (UCB Pharma) (PoM)

Solution, lidocaine hydrochloride 40 mg/mL (4%), net price per unit (4-mL vial and disposable sterile cannula with cover and vial injector) = £5.10

Note May be difficult to obtain

Dose

Anaesthesia of mucous membranes of oropharynx, trachea, and respiratory tract

Child up to 0.075 mL/kg (3 mg/kg) as a single dose sprayed, instilled (if a cavity) or applied with a swab; reduce dose according to size, age, and condition of child, max. 5 mL (200 mg)

LMX 4® (Ferndale)

Cream, lidocaine 4%, net price 5-g tube = £2.98, 30-g tube = £14.90; 12 × 5-g tube with 24 waterproof dressings = £38.16

Excipients include benzyl alcohol and propylene glycol

Dose

Anaesthesia before venous cannulation or venepuncture

Child 1 month–18 years apply thick layer (1–2.5 g; child under 1 year max. 1 g) to small area (2.5 cm × 2.5 cm) of

non-irritated skin at least 30 minutes before procedure; may be applied under an occlusive dressing; max. application time 5 hours (child 1–3 months, 60 minutes; child 3 months–1 year, 4 hours); remove cream with gauze and perform procedure after approximately 5 minutes

Xylocaine® (AstraZeneca)

Spray, lidocaine 10% (100 mg/g) supplying 10 mg lidocaine/dose; 500 spray doses per container, net price 50-mL bottle = £6.29

Dose

Bronchoscopy, laryngoscopy, oesophagoscopy, endotracheal intubation

Child up to 18 years up to 3 mg/kg

With prilocaine

For prescribing information on prilocaine, see p. 658.

EMLA® (AstraZeneca)

Cream, lidocaine 2.5%, prilocaine 2.5%, net price 5-g tube = £2.25; 30-g tube (surgical pack) = £12.30; 5 × 5-g tube with 12 occlusive dressings (premedication pack) = £11.70

Contra-indications use in child less than 37 weeks corrected gestational age

Dose

Anaesthesia before minor skin procedures including venepuncture

Neonate apply max. 1 g under occlusive dressing for max. 1 hour before procedure; max. 1 dose in 24 hours

Child 1–3 months apply max. 1 g under occlusive dressing for max. 1 hour before procedure; max. 1 dose in 24 hours

Child 3 months–1 year apply max. 2 g under occlusive dressing for max. 4 hours before procedure; max. 2 doses in 24 hours

Child 1–18 years apply thick layer under occlusive dressing 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting); max. 2 doses in 24 hours for child 1–12 years

Note Shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca)

Lidocaine for ear, nose, and oropharyngeal use

For prescribing information on phenylephrine, see section 2.7.2.

Lidocaine with phenylephrine (Non-proprietary)

Topical solution, lidocaine hydrochloride 5%, phenylephrine hydrochloride 0.5%, net price 2.5 mL (with nasal applicator) = £11.48

Dose

Anaesthesia before nasal surgery, endoscopy, laryngoscopy, or removal of foreign bodies from the nose

Child 12–18 years up to max. 8 sprays

Mepivacaine

Mepivacaine is an amide-type local anaesthetic used for dental anaesthesia (see Dental Anaesthesia, p. 655).

MEPIVACAINE HYDROCHLORIDE

Cautions see Cautions of Local Anaesthetics, p. 655

Contra-indications see Contra-indications of Local Anaesthetics, p. 655

Hepatic impairment use with caution; increased risk of side-effects in severe impairment

Renal impairment use with caution; increased risk of side-effects

Pregnancy use with caution in early pregnancy

Breast-feeding use with caution

Side-effects see Toxicity and Side-effects, p. 655

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Infiltration anaesthesia and nerve block in dentistry

Child 3–18 years consult expert dental sources

Scandonest® 3% Plain (Septodont) (PoM)

Injection, mepivacaine hydrochloride 30 mg/mL, net price 2.2-mL cartridge = 36p

With adrenaline

For prescribing information on adrenaline, see section 2.7.2; see Use of Vasoconstrictors, p. 654.

Scandonest® 2% Special (Septodont) (PoM)

Injection, mepivacaine hydrochloride 20 mg/mL, adrenaline 1 in 100 000 (10 micrograms/mL), net price 2.2-mL cartridge = 36p

Excipients include sulfites

Prilocaine

Prilocaine is a local anaesthetic of low toxicity which is similar to lidocaine. If used in high doses, methaemoglobinemia may occur, which can be treated with an intravenous injection of **methylthionium chloride** (see Emergency Treatment of Poisoning, p. 24); neonates and infants under 6 months are particularly susceptible to methaemoglobinemia.

PRILOCAINE HYDROCHLORIDE

Cautions see Cautions of Local Anaesthetics, p. 655; severe or untreated hypertension; concomitant drugs which cause methaemoglobinemia; acute porphyria (section 9.8.2); **interactions:** Appendix 1 (prilocaine)

Contra-indications see Contra-indications of Local Anaesthetics, p. 655; anaemia, or congenital or acquired methaemoglobinemia

Hepatic impairment use with caution; lower doses may be required for intrathecal anaesthesia

Renal impairment use with caution; lower doses may be required for intrathecal anaesthesia

Pregnancy large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block; avoid paracervical or pudendal block in obstetrics (neonatal methaemoglobinemia reported); use lower doses for intrathecal use during late pregnancy

Breast-feeding present in milk but not known to be harmful

Side-effects see notes above and Toxicity and Side-effects, p. 655; also hypertension

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Infiltration anaesthesia (higher strengths for dental use only), nerve block

See under preparations below, seek expert advice—**important**: see also under Administration, p. 654

Citanest 1%® (AstraZeneca) (PoM)

Injection, prilocaine hydrochloride 10 mg/mL, net price 50-mL multidose vial = £5.06

Dose

Child 6 months–12 years up to 5 mg/kg adjusted according to site of administration and response; max. 400 mg

Child 12–18 years 100–200 mg/minute, or in incremental doses, to max. total dose 400 mg (adjusted according to site of administration and response)

■ With lidocaine

See Lidocaine, p. 658

■ For dental use

Note Consult expert dental sources for specific advice in relation to dose of prilocaine for dental anaesthesia

Citanest 3% with Octapressin® (Dentsply) (PoM)

Injection, prilocaine hydrochloride 30 mg/mL, felypressin 0.03 unit/mL, net price 2.2-mL cartridge and self-aspirating cartridge (both) = 47p

Ropivacaine

Ropivacaine is an amide-type local anaesthetic agent similar to bupivacaine. It is less cardiotoxic than bupivacaine, but also less potent.

ROPIVACAINE HYDROCHLORIDE

Cautions see Cautions of Local Anaesthetics, p. 655; also acute porphyria (section 9.8.2); **interactions**: Appendix 1 (ropivacaine)

Contra-indications see Contra-indications of Local Anaesthetics, p. 655

Hepatic impairment use with caution in severe impairment

Renal impairment use with caution in severe impairment; increased risk of systemic toxicity in chronic renal failure

Pregnancy not known to be harmful; do not use for paracervical block in obstetrics

Breast-feeding not known to be harmful

Side-effects see Toxicity and Side-effects, p. 655; also hypertension, pyrexia; *less commonly* syncope and hyperthermia

Licensed use 2 mg/mL strength not licensed for use in children under 12 years except for acute pain management by caudal epidural block and continuous epidural infusion; 7.5 mg/mL and 10 mg/mL strengths not licensed for use in children under 12 years

Indications and dose

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Adjust according to child's physical status and nature of procedure, seek expert advice—**important**: see also under Administration, p. 654

Ropivacaine (Non-proprietary) (PoM)

Injection, ropivacaine hydrochloride 2 mg/mL, net price 10 mL = £1.65; 7.5 mg/mL, 10 mL = £2.50; 10 mg/mL, 10 mL = £3.00

Infusion, ropivacaine hydrochloride 2 mg/mL, net price 200 mL = £13.70

Naropin® (AstraZeneca) (PoM)

Injection, ropivacaine hydrochloride 2 mg/mL, net price 10-mL *Polyamp*® = £1.37; 7.5 mg/mL, 10-mL *Polyamp*® = £2.65; 10 mg/mL, 10-mL *Polyamp*® = £3.20

Electrolytes Na⁺ < 0.5 mmol/mL

Infusion, ropivacaine hydrochloride 2 mg/mL, net price 200-mL *Polybag*® = £17.34

Electrolytes Na⁺ < 0.5 mmol/mL

Tetracaine

Tetracaine, a para-aminobenzoic acid ester, is an effective local anaesthetic for topical application; a 4% gel is indicated for anaesthesia before venepuncture or venous cannulation. Tetracaine is effective for 4–6 hours after a single application in most children. It is not recommended prior to neonatal heel lancing.

Tetracaine is rapidly absorbed from mucous membranes and should **never** be applied to inflamed, traumatised, or highly vascular surfaces. It should **never** be used to provide anaesthesia for bronchoscopy or cystoscopy because lidocaine is a safer alternative.

TETRACAINE
(Amethocaine)

Cautions see Cautions of Local Anaesthetics, p. 655

Contra-indications see Contra-indications of Local Anaesthetics, p. 655

Breast-feeding not known to be harmful

Side-effects see Toxicity and Side-effects, p. 655

Important Rapid and extensive absorption may result in systemic side-effects (see also notes above)

Licensed use not licensed for use in neonates

Indications and dose

Anaesthesia before venepuncture or venous cannulation see preparation below

Eye section 11.7

Ametop® (S&N Hlth.)

Gel, tetracaine 4%, net price 1.5-g tube = £1.08

Excipients include hydroxybenzoates (parabens)

Dose

Neonate apply contents of tube (or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation

Child 1 month–18 years apply contents of tube (or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation

Note Child 5–18 years, contents of max. 5 tubes applied at separate sites at a single time, child 1 month–5 years, contents of max. 1 tube applied at separate sites at a single time

A1 Interactions

Two or more drugs given at the same time may exert their effects independently or may interact. The interaction may be potentiation or antagonism of one drug by another, or occasionally some other effect. Adverse drug interactions should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA), through the Yellow Card Scheme (see Adverse Reactions to Drugs, p. 11), as for other adverse drug reactions.

Drug interactions may be **pharmacodynamic** or **pharmacokinetic**.

Pharmacodynamic interactions

These are interactions between drugs which have similar or antagonistic pharmacological effects or side-effects. They may be due to competition at receptor sites, or occur between drugs acting on the same physiological system. They are usually predictable from a knowledge of the pharmacology of the interacting drugs; in general, those demonstrated with one drug are likely to occur with related drugs. They occur to a greater or lesser extent in most patients who receive the interacting drugs.

Pharmacokinetic interactions

These occur when one drug alters the absorption, distribution, metabolism, or excretion of another, thus increasing or reducing the amount of drug available to produce its pharmacological effects. They are not easily predicted and many of them affect only a small proportion of patients taking the combination of drugs. Pharmacokinetic interactions occurring with one drug cannot be assumed to occur with related drugs unless their pharmacokinetic properties are known to be similar.

Pharmacokinetic interactions are of several types:

Affecting absorption The rate of absorption or the total amount absorbed can both be altered by drug interactions. Delayed absorption is rarely of clinical importance unless high peak plasma concentrations are required (e.g. when giving an analgesic). Reduction in the total amount absorbed, however, may result in ineffective therapy.

Due to changes in protein binding To a variable extent most drugs are loosely bound to plasma proteins. Protein-binding sites are non-specific and one drug can displace another thereby increasing its proportion free to diffuse from plasma to its site of action. This only produces a detectable increase in effect if it is an extensively bound drug (more than 90%) that is not widely distributed throughout the body. Even so displacement rarely produces more than transient potentiation because this increased concentration of free drug results in an increased rate of elimination.

Displacement from protein binding plays a part in the potentiation of warfarin by sulfonamides, and tolbutamide but the importance of these interactions is due

mainly to the fact that warfarin metabolism is also inhibited.

Affecting metabolism Many drugs are metabolised in the liver. Induction of the hepatic microsomal enzyme system by one drug can gradually increase the rate of metabolism of another, resulting in lower plasma concentrations and a reduced effect. On withdrawal of the inducer plasma concentrations increase and toxicity may occur. Barbiturates, griseofulvin, many antiepileptics, and rifampicin are the most important enzyme inducers. Drugs affected include warfarin and the oral contraceptives.

Conversely when one drug inhibits the metabolism of another higher plasma concentrations are produced, rapidly resulting in an increased effect with risk of toxicity. Some drugs which potentiate warfarin and phenytoin do so by this mechanism.

Isoenzymes of the hepatic cytochrome P450 system interact with a wide range of drugs. Drugs may be substrates, inducers or inhibitors of the different isoenzymes. A great deal of *in-vitro* information is available on the effect of drugs on the isoenzymes; however, since drugs are eliminated by a number of different metabolic routes as well as renal excretion, the clinical effects of interactions cannot be predicted accurately from laboratory data on the cytochrome P450 isoenzymes. Except where a combination of drugs is specifically contra-indicated, the BNFC presents only interactions that have been reported in clinical practice. In all cases the possibility of an interaction must be considered if toxic effects occur or if the activity of a drug diminishes.

Affecting renal excretion Drugs are eliminated through the kidney both by glomerular filtration and by active tubular secretion. Competition occurs between those which share active transport mechanisms in the proximal tubule. For example, salicylates and some other NSAIDs delay the excretion of methotrexate; serious methotrexate toxicity is possible.

Relative importance of interactions

Many drug interactions are harmless and many of those which are potentially harmful only occur in a small proportion of patients; moreover, the severity of an interaction varies from one patient to another. Drugs with a small therapeutic ratio (e.g. phenytoin) and those which require careful control of dosage (e.g. anticoagulants, antihypertensives, and antidiabetics) are most often involved.

Patients at increased risk from drug interactions include those with impaired renal or liver function.

Serious interactions The symbol ● has been placed against interactions that are **potentially serious** and where concomitant administration of the drugs involved should be **avoided** (or only undertaken with caution and appropriate monitoring).

Interactions that have no symbol do not usually have serious consequences.

List of drug interactions

The following is an alphabetical list of drugs and their interactions; to avoid excessive cross-referencing each drug or group is listed twice: in the alphabetical list and also against the drug or group with which it interacts. For explanation of symbol ● see above

Abacavir

- Analgesics: abacavir possibly reduces plasma concentration of **methadone**
- Antibacterials: plasma concentration of abacavir possibly reduced by **rifampicin**
- Antiepileptics: plasma concentration of abacavir possibly reduced by **phenobarbital** and **phenytoin**
- Antivirals: abacavir possibly reduces effects of ●**ribavirin**; plasma concentration of abacavir reduced by ●**tipranavir**
- Orlistat: absorption of abacavir possibly reduced by ●**orlistat**

Abatacept

- Adalimumab: increased risk of side-effects when abatacept given with **adalimumab**
- Certolizumab pegol: avoid concomitant use of abatacept with ●**certolizumab pegol**
- Etanercept: avoid concomitant use of abatacept with ●**etanercept**
- Golimumab: avoid concomitant use of abatacept with ●**golimumab**
- Infliximab: avoid concomitant use of abatacept with ●**infliximab**
- Vaccines: avoid concomitant use of abatacept with live ●**vaccines** (see p. 604)

Abiraterone

- Antibacterials: plasma concentration of abiraterone possibly reduced by ●**rifabutin**—manufacturer of abiraterone advises avoid concomitant use; plasma concentration of abiraterone reduced by ●**rifampicin**—manufacturer of abiraterone advises avoid concomitant use
- Antidepressants: plasma concentration of abiraterone possibly reduced by ●**St John's wort**—manufacturer of abiraterone advises avoid concomitant use
- Antiepileptics: plasma concentration of abiraterone possibly reduced by ●**carbamazepine**, ●**phenobarbital** and ●**phenytoin**—manufacturer of abiraterone advises avoid concomitant use

Acarbose *see* Antidiabetics

ACE Inhibitors

- Alcohol: enhanced hypotensive effect when ACE inhibitors given with **alcohol**
- Aldesleukin: enhanced hypotensive effect when ACE inhibitors given with **aldesleukin**
- Aliskiren: avoid concomitant use of ACE inhibitors with ●**aliskiren** (see also under Renin inhibitors, BNF section 2.5.5.3)
- Allopurinol: manufacturers state possible increased risk of leucopenia and hypersensitivity reactions when ACE inhibitors given with **allopurinol** especially in renal impairment
- Alpha-blockers: enhanced hypotensive effect when ACE inhibitors given with **alpha-blockers**
- Anaesthetics, General: enhanced hypotensive effect when ACE inhibitors given with **general anaesthetics**
- Analgesics: increased risk of renal impairment when ACE inhibitors given with **NSAIDs**, also hypotensive effect antagonised
- Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when ACE inhibitors given with **angiotensin-II receptor antagonists**

ACE Inhibitors (*continued*)

- Antacids: absorption of ACE inhibitors possibly reduced by **antacids**; absorption of captopril, enalapril and fosinopril reduced by **antacids**
- Antibacterials: plasma concentration of active metabolite of imidapril reduced by **rifampicin** (reduced antihypertensive effect); quinapril tablets reduce absorption of **tetracyclines** (quinapril tablets contain magnesium carbonate); possible increased risk of hyperkalaemia when ACE inhibitors given with **trimethoprim**
- Anticoagulants: increased risk of hyperkalaemia when ACE inhibitors given with **heparins**
- Antidepressants: hypotensive effect of ACE inhibitors possibly enhanced by **MAOIs**
- Antidiabetics: ACE inhibitors possibly enhance hypoglycaemic effect of **insulin**, **metformin** and **sulfonylureas**
- Antipsychotics: enhanced hypotensive effect when ACE inhibitors given with **antipsychotics**
- Anxiolytics and Hypnotics: enhanced hypotensive effect when ACE inhibitors given with **anxiolytics** and **hypnotics**
- Azathioprine: increased risk of anaemia or leucopenia when captopril given with **azathioprine** especially in renal impairment; increased risk of anaemia when enalapril given with **azathioprine** especially in renal impairment
- Beta-blockers: enhanced hypotensive effect when ACE inhibitors given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when ACE inhibitors given with **calcium-channel blockers**
- Cardiac Glycosides: captopril possibly increases plasma concentration of **digoxin**
- Ciclosporin: increased risk of hyperkalaemia when ACE inhibitors given with ●**ciclosporin**
- Clonidine: enhanced hypotensive effect when ACE inhibitors given with **clonidine**; antihypertensive effect of captopril possibly delayed by previous treatment with **clonidine**
- Corticosteroids: hypotensive effect of ACE inhibitors antagonised by **corticosteroids**
- Diazoxide: enhanced hypotensive effect when ACE inhibitors given with **diazoxide**
- Diuretics: enhanced hypotensive effect when ACE inhibitors given with ●**diuretics**; increased risk of severe hyperkalaemia when ACE inhibitors given with ●**potassium-sparing diuretics** and **aldosterone antagonists**
- Dopaminergics: enhanced hypotensive effect when ACE inhibitors given with **levodopa**
- Gold: flushing and hypotension reported when ACE inhibitors given with ●**sodium aurothiomalate**
- Lithium: ACE inhibitors reduce excretion of ●**lithium** (increased plasma concentration)
- Methyldopa: enhanced hypotensive effect when ACE inhibitors given with **methyldopa**
- Moxisylyte: enhanced hypotensive effect when ACE inhibitors given with **moxisylyte**
- Moxonidine: enhanced hypotensive effect when ACE inhibitors given with **moxonidine**
- Muscle Relaxants: enhanced hypotensive effect when ACE inhibitors given with **baclofen** or **tizanidine**
- Nitrates: enhanced hypotensive effect when ACE inhibitors given with **nitrates**
- Oestrogens: hypotensive effect of ACE inhibitors antagonised by **oestrogens**
- Potassium Salts: increased risk of severe hyperkalaemia when ACE inhibitors given with ●**potassium salts**
- Probenecid: excretion of captopril reduced by **probenecid**
- Prostaglandins: enhanced hypotensive effect when ACE inhibitors given with **alprostadiol**

ACE Inhibitors (*continued*)

Vasodilator Antihypertensives: enhanced hypotensive effect when ACE inhibitors given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Acebutolol *see* Beta-blockers

Aceclofenac *see* NSAIDs

Acemetacin *see* NSAIDs

Acenocoumarol *see* Coumarins

Acetazolamide *see* Diuretics

Aciclovir

Note Interactions do not apply to topical aciclovir preparations

Note Valaciclovir interactions as for aciclovir

Ciclosporin: increased risk of nephrotoxicity when aciclovir given with **ciclosporin**

Mycophenolate: plasma concentration of aciclovir increased by **mycophenolate**, also plasma concentration of inactive metabolite of mycophenolate increased

Probenecid: excretion of aciclovir reduced by **probenecid** (increased plasma concentration)

Tacrolimus: possible increased risk of nephrotoxicity when aciclovir given with **tacrolimus**

Theophylline: aciclovir possibly increases plasma concentration of **theophylline**

Acitretin *see* Retinoids

Acrivastine *see* Antihistamines

Adalimumab

Abatacept: increased risk of side-effects when adalimumab given with **abatacept**

- Anakinra: avoid concomitant use of adalimumab with **anakinra**

- Vaccines: avoid concomitant use of adalimumab with live **vaccines** (see p. 604)

Adefovir

Antivirals: avoidance of adefovir advised by manufacturer of **tenofovir**

Interferons: manufacturer of adefovir advises caution with **peginterferon alfa**

Adenosine

Note Possibility of interaction with drugs tending to impair myocardial conduction

Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with **bupivacaine**, **levobupivacaine**, **prilocaine** or **ropivacaine**

- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other **anti-arrhythmics**
- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with **antipsychotics** that prolong the QT interval

- Beta-blockers: increased myocardial depression when anti-arrhythmics given with **beta-blockers**

Caffeine citrate: anti-arrhythmic effect of adenosine antagonised by **caffeine citrate**—manufacturer of adenosine advises avoid caffeine citrate for at least 12 hours before adenosine

- Dipyridamole: effect of adenosine enhanced and extended by **dipyridamole** (important risk of toxicity)—reduce dose of adenosine, see Dose under Adenosine, p. 82

Nicotine: effects of adenosine possibly enhanced by **nicotine**

Theophylline: anti-arrhythmic effect of adenosine antagonised by **theophylline**—manufacturer of adenosine advises avoid theophylline for 24 hours before adenosine

Adrenaline (epinephrine) *see* Sympathomimetics

Adrenergic Neurone Blockers

Alcohol: enhanced hypotensive effect when adrenergic neurone blockers given with **alcohol**

Alpha-blockers: enhanced hypotensive effect when adrenergic neurone blockers given with **alpha-blockers**

Adrenergic Neurone Blockers (*continued*)

- Anaesthetics, General: enhanced hypotensive effect when adrenergic neurone blockers given with **general anaesthetics**

Analgesics: hypotensive effect of adrenergic neurone blockers antagonised by **NSAIDs**

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when adrenergic neurone blockers given with **angiotensin-II receptor antagonists**

Antidepressants: enhanced hypotensive effect when adrenergic neurone blockers given with **MAOIs**; hypotensive effect of adrenergic neurone blockers antagonised by **tricyclics**

Antipsychotics: hypotensive effect of adrenergic neurone blockers antagonised by **haloperidol**; hypotensive effect of adrenergic neurone blockers antagonised by higher doses of **chlorpromazine**; enhanced hypotensive effect when adrenergic neurone blockers given with **phenothiazines**

Anxiolytics and Hypnotics: enhanced hypotensive effect when adrenergic neurone blockers given with **anxiolytics** and **hypnotics**

Beta-blockers: enhanced hypotensive effect when adrenergic neurone blockers given with **beta-blockers**

Calcium-channel Blockers: enhanced hypotensive effect when adrenergic neurone blockers given with **calcium-channel blockers**

Clonidine: enhanced hypotensive effect when adrenergic neurone blockers given with **clonidine**

Corticosteroids: hypotensive effect of adrenergic neurone blockers antagonised by **corticosteroids**

Diazoxide: enhanced hypotensive effect when adrenergic neurone blockers given with **diazoxide**

Diuretics: enhanced hypotensive effect when adrenergic neurone blockers given with **diuretics**

Dopaminergics: enhanced hypotensive effect when adrenergic neurone blockers given with **levodopa**

Methyldopa: enhanced hypotensive effect when adrenergic neurone blockers given with **methyldopa**

Moxisylyte: enhanced hypotensive effect when adrenergic neurone blockers given with **moxisylyte**

Moxonidine: enhanced hypotensive effect when adrenergic neurone blockers given with **moxonidine**

Muscle Relaxants: enhanced hypotensive effect when adrenergic neurone blockers given with **baclofen** or **tizanidine**

Nitrates: enhanced hypotensive effect when adrenergic neurone blockers given with **nitrates**

Oestrogens: hypotensive effect of adrenergic neurone blockers antagonised by **oestrogens**

Pizotifen: hypotensive effect of adrenergic neurone blockers antagonised by **pizotifen**

Prostaglandins: enhanced hypotensive effect when adrenergic neurone blockers given with **alprostadil**

- Sympathomimetics: hypotensive effect of guanethidine antagonised by **dexamfetamine** and **lisdex-amfetamine**; hypotensive effect of adrenergic neurone blockers antagonised by **ephedrine**, **isometheptene**, **metaraminol**, **methylphenidate**, **noradrenaline (norepinephrine)**, **oxymetazoline**, **phenylephrine**, **pseudoephedrine** and **xylometazoline**

Vasodilator Antihypertensives: enhanced hypotensive effect when adrenergic neurone blockers given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Adsorbents *see* Kaolin

Afatinib

Anti-arrhythmics: plasma concentration of afatinib possibly increased by **amiodarone**—manufacturer of afatinib advises separating administration of amiodarone by 6 to 12 hours

Antibacterials: plasma concentration of afatinib possibly increased by **erythromycin**—manufacturer of afatinib advises separating administration of erythromycin by 6 to 12 hours; plasma concentration of afatinib reduced by **rifampicin**

Afatinib (*continued*)

Antifungals: plasma concentration of afatinib possibly increased by **itraconazole**—manufacturer of afatinib advises separating administration of itraconazole by 6 to 12 hours

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Antivirals: plasma concentration of afatinib increased by **ritonavir**—manufacturer of afatinib advises separating administration of ritonavir by 6 to 12 hours; plasma concentration of afatinib possibly increased by **saquinavir**—manufacturer of afatinib advises separating administration of saquinavir by 6 to 12 hours
- Calcium-channel Blockers: plasma concentration of afatinib possibly increased by **verapamil**—manufacturer of afatinib advises separating administration of verapamil by 6 to 12 hours
- Ciclosporin: plasma concentration of afatinib possibly increased by **ciclosporin**—manufacturer of afatinib advises separating administration of ciclosporin by 6 to 12 hours
- Tacrolimus: plasma concentration of afatinib possibly increased by **tacrolimus**—manufacturer of afatinib advises separating administration of tacrolimus by 6 to 12 hours

Agalsidase Alfa and Beta

Anti-arrhythmics: effects of agalsidase alfa and beta possibly inhibited by **amiodarone** (manufacturers of agalsidase alfa and beta advise avoid concomitant use)

Antibacterials: effects of agalsidase alfa and beta possibly inhibited by **gentamicin** (manufacturers of agalsidase alfa and beta advise avoid concomitant use)

Antimalarials: effects of agalsidase alfa and beta possibly inhibited by **chloroquine** and **hydroxychloroquine** (manufacturers of agalsidase alfa and beta advise avoid concomitant use)

Agomelatine

- Antibacterials: manufacturer of agomelatine advises avoid concomitant use with **ciprofloxacin**
- Antidepressants: metabolism of agomelatine inhibited by **fluvoxamine** (increased plasma concentration)
- Antimalarials: avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperazine with arteminol**
- Atomoxetine: possible increased risk of convulsions when antidepressants given with **atomoxetine**

Alcohol

ACE Inhibitors: enhanced hypotensive effect when alcohol given with **ACE inhibitors**

Adrenergic Neurone Blockers: enhanced hypotensive effect when alcohol given with **adrenergic neurone blockers**

Alpha-blockers: increased sedative effect when alcohol given with **indoramin**; enhanced hypotensive effect when alcohol given with **alpha-blockers**

Analgesics: enhanced hypotensive and sedative effects when alcohol given with **opioid analgesics**

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when alcohol given with **angiotensin-II receptor antagonists**

- Antibacterials: disulfiram-like reaction when alcohol given with **metronidazole**; possibility of disulfiram-like reaction when alcohol given with **tinidazole**; increased risk of convulsions when alcohol given with **cycloserine**
- Anticoagulants: major changes in consumption of alcohol may affect anticoagulant control with **coumarins** or **phenindione**
- Antidepressants: some beverages containing alcohol and some dealcoholised beverages contain tyramine which interacts with **MAOIs** (hypertensive crisis)—if no tyramine, enhanced hypotensive effect; sedative effects possibly increased when alcohol given

Alcohol• Antidepressants (*continued*)

- with **SSRIs**; increased sedative effect when alcohol given with **mirtazapine**, **tricyclic-related antidepressants** or **tricyclics**
- Antidiabetics: alcohol enhances hypoglycaemic effect of **antidiabetics**; increased risk of lactic acidosis when alcohol given with **metformin**
- Antiepileptics: alcohol possibly increases CNS side-effects of **carbamazepine**; increased sedative effect when alcohol given with **phenobarbital**; chronic heavy consumption of alcohol possibly reduces plasma concentration of **phenytoin**; increased risk of blurred vision when alcohol given with **retigabine**
- Antifungals: effects of alcohol possibly enhanced by **griseofulvin**
- Antihistamines: increased sedative effect when alcohol given with **antihistamines** (possibly less effect with non-sedating antihistamines)
- Antimuscarinics: increased sedative effect when alcohol given with **hyoscine**
- Antipsychotics: increased sedative effect when alcohol given with **antipsychotics**
- Anxiolytics and Hypnotics: increased sedative effect when alcohol given with **anxiolytics and hypnotics**
- Beta-blockers: enhanced hypotensive effect when alcohol given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when alcohol given with **calcium-channel blockers**; plasma concentration of alcohol possibly increased by **verapamil**
- Clonidine: enhanced hypotensive effect when alcohol given with **clonidine**
- Cytotoxics: disulfiram-like reaction when alcohol given with **procarbazine**
- Dapoxetine: increased sedative effect when alcohol given with **dapoxetine**
- Diazoxide: enhanced hypotensive effect when alcohol given with **diazoxide**
- Disulfiram: disulfiram reaction when alcohol given with **disulfiram** (see BNF section 4.10.1)
- Diuretics: enhanced hypotensive effect when alcohol given with **diuretics**
- Dopaminergics: alcohol reduces tolerance to **bromocriptine**
- Levamisole: possibility of disulfiram-like reaction when alcohol given with **levamisole**
- Lipid-regulating Drugs: avoidance of alcohol advised by manufacturer of **lomitapide**
- Lofexidine: increased sedative effect when alcohol given with **lofexidine**
- Methyldopa: enhanced hypotensive effect when alcohol given with **methyldopa**
- Metoclopramide: absorption of alcohol possibly increased by **metoclopramide**
- Moxonidine: enhanced hypotensive effect when alcohol given with **moxonidine**
- Muscle Relaxants: increased sedative effect when alcohol given with **baclofen**, **methocarbamol** or **tizanidine**
- Nicorandil: alcohol possibly enhances hypotensive effect of **nicorandil**
- Nitrates: enhanced hypotensive effect when alcohol given with **nitrates**
- Paraldehyde: increased sedative effect when alcohol given with **paraldehyde**
- Retinoids: presence of alcohol causes etretinate to be formed from **acitretin** (increased risk of teratogenicity in women of child-bearing potential)
- Sympathomimetics: alcohol possibly enhances effects of **methylphenidate**
- Vasodilator Antihypertensives: enhanced hypotensive effect when alcohol given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Aldesleukin

- ACE Inhibitors: enhanced hypotensive effect when aldesleukin given with **ACE inhibitors**
- Alpha-blockers: enhanced hypotensive effect when aldesleukin given with **alpha-blockers**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when aldesleukin given with **angiotensin-II receptor antagonists**
- Antivirals: aldesleukin possibly increases plasma concentration of **indinavir**
- Beta-blockers: enhanced hypotensive effect when aldesleukin given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when aldesleukin given with **calcium-channel blockers**
- Clonidine: enhanced hypotensive effect when aldesleukin given with **clonidine**
- Corticosteroids: manufacturer of aldesleukin advises avoid concomitant use with **corticosteroids**
 - Cytotoxics: manufacturer of aldesleukin advises avoid concomitant use with **cisplatin**, **dacarbazine** and **vinblastine**
- Diazoxide: enhanced hypotensive effect when aldesleukin given with **diazoxide**
- Diuretics: enhanced hypotensive effect when aldesleukin given with **diuretics**
- Methyldopa: enhanced hypotensive effect when aldesleukin given with **methyldopa**
- Moxonidine: enhanced hypotensive effect when aldesleukin given with **moxonidine**
- Nitrates: enhanced hypotensive effect when aldesleukin given with **nitrates**
- Vasodilator Antihypertensives: enhanced hypotensive effect when aldesleukin given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Alendronic Acid *see* Bisphosphonates

Alfentanil *see* Opioid Analgesics

Alfuzosin *see* Alpha-blockers

Alimemazine *see* Antihistamines

Aliskiren

- ACE Inhibitors: avoid concomitant use of aliskiren with **ACE inhibitors** (see also under Renin inhibitors, BNF section 2.5.5.3)
- Analgesics: hypotensive effect of aliskiren possibly antagonised by **NSAIDs**
- Angiotensin-II Receptor Antagonists: avoid concomitant use of aliskiren with **angiotensin-II receptor antagonists** (see also under Renin inhibitors, BNF section 2.5.5.3); plasma concentration of aliskiren possibly reduced by **irbesartan**
- Antibacterials: plasma concentration of aliskiren reduced by **rifampicin**
- Anticoagulants: increased risk of hyperkalaemia when aliskiren given with **heparins**
- Antifungals: plasma concentration of aliskiren increased by **itraconazole**—avoid concomitant use
- Calcium-channel Blockers: plasma concentration of aliskiren increased by **verapamil**
- Ciclosporin: plasma concentration of aliskiren increased by **ciclosporin**—avoid concomitant use
- Diuretics: aliskiren reduces plasma concentration of **furosemide**; increased risk of hyperkalaemia when aliskiren given with **potassium-sparing diuretics** and **aldosterone antagonists**
- Grapefruit Juice: plasma concentration of aliskiren reduced by **grapefruit juice**—avoid concomitant use
- Potassium Salts: increased risk of hyperkalaemia when aliskiren given with **potassium salts**

Alitretinoin *see* Retinoids

Alkylating Drugs *see* Bendamustine, Busulfan, Carmustine, Cyclophosphamide, Estramustine, Ifosfamide, Lomustine, Melphalan, and Thiotepa

Allopurinol

ACE Inhibitors: manufacturers state possible increased risk of leucopenia and hypersensitivity reactions

Allopurinol

ACE Inhibitors (*continued*)

when allopurinol given with **ACE inhibitors** especially in renal impairment

Antibacterials: increased risk of rash when allopurinol given with **amoxicillin** or **ampicillin**

Anticoagulants: allopurinol possibly enhances anticoagulant effect of **coumarins**

- Antivirals: allopurinol increases plasma concentration of **didanosine** (risk of toxicity)—avoid concomitant use
 - Azathioprine: allopurinol enhances effects and increases toxicity of **azathioprine** (reduce dose of azathioprine to one quarter of usual dose)
- Ciclosporin: allopurinol possibly increases plasma concentration of **ciclosporin** (risk of nephrotoxicity)
- Cytotoxics: allopurinol enhances effects and increases toxicity of **mercaptopurine** (reduce dose of mercaptopurine to one quarter of usual dose); avoidance of allopurinol advised by manufacturer of **capecitabine**
- Diuretics: increased risk of hypersensitivity when allopurinol given with **thiazides and related diuretics** especially in renal impairment
- Theophylline: allopurinol possibly increases plasma concentration of **theophylline**

Almotriptan *see* 5HT₁-receptor Agonists (under HT)

Allogliptin *see* Antidiabetics

Alpha₂-adrenoceptor Stimulants *see* Apraclonidine, Brimonidine, Clonidine, and Methyldopa

Alpha-blockers

- ACE Inhibitors: enhanced hypotensive effect when alpha-blockers given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when alpha-blockers given with **adrenergic neurone blockers**
- Alcohol: enhanced hypotensive effect when alpha-blockers given with **alcohol**; increased sedative effect when indoramin given with **alcohol**
- Aldesleukin: enhanced hypotensive effect when alpha-blockers given with **aldesleukin**
- Anaesthetics, General: enhanced hypotensive effect when alpha-blockers given with **general anaesthetics**
- Analgesics: hypotensive effect of alpha-blockers antagonised by **NSAIDs**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when alpha-blockers given with **angiotensin-II receptor antagonists**
- Antidepressants: enhanced hypotensive effect when alpha-blockers given with **MAOIs**; manufacturer of indoramin advises avoid concomitant use with **MAOIs**
- Antipsychotics: enhanced hypotensive effect when alpha-blockers given with **antipsychotics**
- Antivirals: plasma concentration of alfuzosin possibly increased by **ritonavir**—avoid concomitant use; avoidance of alfuzosin advised by manufacturer of **telaprevir**
- Anxiolytics and Hypnotics: enhanced hypotensive and sedative effects when alpha-blockers given with **anxiolytics and hypnotics**
- Beta-blockers: enhanced hypotensive effect when alpha-blockers given with **beta-blockers**, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Calcium-channel Blockers: enhanced hypotensive effect when alpha-blockers given with **calcium-channel blockers**, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin; plasma concentration of tamsulosin increased by **verapamil**
- Cardiac Glycosides: prazosin increases plasma concentration of **digoxin**
- Clonidine: enhanced hypotensive effect when alpha-blockers given with **clonidine**

Alpha-blockers (continued)

- Cobicistat: plasma concentration of alfuzosin possibly increased by **●cobicistat**—manufacturer of cobicistat advises avoid concomitant use
- Corticosteroids: hypotensive effect of alpha-blockers antagonised by **corticosteroids**
- Diazoxide: enhanced hypotensive effect when alpha-blockers given with **diazoxide**
- Diuretics: enhanced hypotensive effect when alpha-blockers given with **●diuretics**, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Dopaminergics: enhanced hypotensive effect when alpha-blockers given with **levodopa**
- Methyldopa: enhanced hypotensive effect when alpha-blockers given with **methyldopa**
- Moxisylyte: possible severe postural hypotension when alpha-blockers given with **●moxisylyte**
- Moxonidine: enhanced hypotensive effect when alpha-blockers given with **moxonidine**
- Muscle Relaxants: enhanced hypotensive effect when alpha-blockers given with **baclofen** or **tizanidine**
- Nitrates: enhanced hypotensive effect when alpha-blockers given with **nitrates**
- Oestrogens: hypotensive effect of alpha-blockers antagonised by **oestrogens**
- Prostaglandins: enhanced hypotensive effect when alpha-blockers given with **alprostadil**
- Sildenafil: enhanced hypotensive effect when alpha-blockers given with **●sildenafil** (avoid alpha-blockers for 4 hours after sildenafil)—see also under Phosphodiesterase type-5 inhibitors, BNF section 7.4.5
- Sympathomimetics: avoid concomitant use of tolazoline with **●adrenaline (epinephrine)** or **●dopamine**
- Tadalafil: enhanced hypotensive effect when alpha-blockers given with **●tadalafil**—see also under Phosphodiesterase type-5 inhibitors, BNF section 7.4.5; enhanced hypotensive effect when doxazosin given with **●tadalafil**—manufacturer of tadalafil advises avoid concomitant use
- Ulcer-healing Drugs: effects of tolazoline antagonised by **●cimetidine** and **●ranitidine**
- Vardenafil: enhanced hypotensive effect when alpha-blockers given with **●vardenafil**—separate doses by 6 hours (except with tamsulosin)—see also under Phosphodiesterase type-5 inhibitors, BNF section 7.4.5
- Vasodilator Antihypertensives: enhanced hypotensive effect when alpha-blockers given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Alpha-blockers (post-synaptic) *see* Alpha-blockers**Alprazolam** *see* Anxiolytics and Hypnotics**Alprostadil** *see* Prostaglandins**Aluminium Hydroxide** *see* Antacids**Amantadine**

- Antimalarials: plasma concentration of amantadine possibly increased by **quinine**
- Antipsychotics: increased risk of extrapyramidal side-effects when amantadine given with **antipsychotics**
- Bupropion: increased risk of side-effects when amantadine given with **bupropion**
- Memantine: increased risk of CNS toxicity when amantadine given with **●memantine** (manufacturer of memantine advises avoid concomitant use); effects of dopaminergics possibly enhanced by **memantine**
- Methyldopa: increased risk of extrapyramidal side-effects when amantadine given with **methyldopa**; antiparkinsonian effect of dopaminergics antagonised by **methyldopa**
- Tetrabenazine: increased risk of extrapyramidal side-effects when amantadine given with **tetrabenazine**

Ambrisentan

- Antibacterials: plasma concentration of ambrisentan possibly increased by **rifampicin**

Ambrisentan (continued)

- Ciclosporin: plasma concentration of ambrisentan increased by **●ciclosporin** (see Dose under Ambrisentan, BNF section 2.5.1)

Amikacin *see* Aminoglycosides**Amiloride** *see* Diuretics**Aminoglycosides**

- Agalsidase Alfa and Beta: gentamicin possibly inhibits effects of **agalsidase alfa and beta** (manufacturers of agalsidase alfa and beta advise avoid concomitant use)
- Analgesics: plasma concentration of amikacin and gentamicin in neonates possibly increased by **indometacin**
- Antibacterials: neomycin reduces absorption of **phenoxymethylpenicillin**; increased risk of nephrotoxicity when aminoglycosides given with **colistimethate sodium** or **polymyxins**; increased risk of nephrotoxicity and ototoxicity when aminoglycosides given with **capreomycin** or **●vancomycin**; possible increased risk of nephrotoxicity when aminoglycosides given with **cephalosporins**
- Anticoagulants: experience in anticoagulant clinics suggests that INR possibly altered when neomycin (given for local action on gut) is given with **●coumarins** or **●phenindione**
- Antidiabetics: neomycin possibly enhances hypoglycaemic effect of **acarbose**, also severity of gastrointestinal effects increased
- Antifungals: increased risk of nephrotoxicity when aminoglycosides given with **amphotericin**
- Bisphosphonates: increased risk of hypocalcaemia when aminoglycosides given with **bisphosphonates**
- Cardiac Glycosides: gentamicin possibly increases plasma concentration of **digoxin**; neomycin reduces absorption of **digoxin**
- Ciclosporin: increased risk of nephrotoxicity when aminoglycosides given with **●ciclosporin**
- Cytotoxics: neomycin possibly reduces absorption of **methotrexate**; neomycin reduces bioavailability of **sorafenib**; increased risk of nephrotoxicity and possibly of ototoxicity when aminoglycosides given with **●platinum compounds**
- Diuretics: increased risk of ototoxicity when aminoglycosides given with **●loop diuretics**
- Mannitol: manufacturer of tobramycin advises avoid concomitant use with **mannitol**
- Muscle Relaxants: aminoglycosides enhance effects of **●non-depolarising muscle relaxants** and **●suxamethonium**
- Parasympathomimetics: aminoglycosides antagonise effects of **●neostigmine** and **●pyridostigmine**
- Tacrolimus: increased risk of nephrotoxicity when aminoglycosides given with **●tacrolimus**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626
- Vitamins: neomycin possibly reduces absorption of **vitamin A**

Aminophylline *see* Theophylline**Aminosalicylates**

- Azathioprine: possible increased risk of leucopenia when aminosalicylates given with **azathioprine**
- Cardiac Glycosides: sulfasalazine possibly reduces absorption of **digoxin**
- Cytotoxics: possible increased risk of leucopenia when aminosalicylates given with **mercaptopurine**
- Folates: sulfasalazine possibly reduces absorption of **folic acid**

Amiodarone

- Note Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped
- Agalsidase Alfa and Beta: amiodarone possibly inhibits effects of **agalsidase alfa and beta** (manufacturers of agalsidase alfa and beta advise avoid concomitant use)

Amiodarone (*continued*)

- Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with **bupivacaine**, **levobupivacaine**, **prilocaine** or **ropivacaine**
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other **anti-arrhythmics**; increased risk of ventricular arrhythmias when amiodarone given with **disopyramide** or **dronedrone**—avoid concomitant use; amiodarone increases plasma concentration of **flecainide** (halve dose of flecainide)
 - Antibacterials: increased risk of ventricular arrhythmias when amiodarone given with **parenteral erythromycin**—avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with **levofloxacin** or **moxifloxacin**—avoid concomitant use; possible increased risk of ventricular arrhythmias when amiodarone given with **sulfamethoxazole** and **trimethoprim** (as co-trimoxazole)—manufacturer of amiodarone advises avoid concomitant use of co-trimoxazole; possible increased risk of ventricular arrhythmias when amiodarone given with **telithromycin**
 - Anticoagulants: amiodarone inhibits metabolism of **coumarins** and **phenindione** (enhanced anticoagulant effect); amiodarone increases plasma concentration of **dabigatran** (see Dose under Dabigatran, BNf section 2.8.2)
 - Antidepressants: avoidance of amiodarone advised by manufacturer of **citalopram** and **escitalopram** (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when amiodarone given with **tricyclics**—avoid concomitant use
 - Antiepileptics: amiodarone inhibits metabolism of **phenytoin** (increased plasma concentration)
 - Antihistamines: increased risk of ventricular arrhythmias when amiodarone given with **mizolastine**—avoid concomitant use
 - Antimalarials: avoidance of amiodarone advised by manufacturer of **piperaquine with arteminol** (possible risk of ventricular arrhythmias); avoidance of amiodarone advised by manufacturer of **artemether with lumefantrine** (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when amiodarone given with **chloroquine** and **hydroxychloroquine**, **mefloquine** or **quinine**—avoid concomitant use
 - Antimuscarinics: increased risk of ventricular arrhythmias when amiodarone given with **tolterodine**
 - Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with **antipsychotics** that prolong the QT interval; increased risk of ventricular arrhythmias when amiodarone given with **benperidol**—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with **amisulpride**, **droperidol**, **haloperidol**, **phenothiazines**, **pimozide** or **zuclopenthixol**—avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with **sulpiride**
 - Antivirals: plasma concentration of amiodarone possibly increased by **atazanavir**; plasma concentration of amiodarone possibly increased by **fosamprenavir** (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of amiodarone possibly increased by **indinavir**—avoid concomitant use; plasma concentration of amiodarone increased by **ritonavir** (increased risk of ventricular arrhythmias—avoid concomitant use); increased risk of ventricular arrhythmias when amiodarone given with **sacquinavir**—avoid concomitant use; avoidance of amiodarone advised by manufacturer of **telaprevir** (risk of ventricular arrhythmias)

Amiodarone (*continued*)

- Atomoxetine: increased risk of ventricular arrhythmias when amiodarone given with **atomoxetine**
 - Beta-blockers: increased risk of bradycardia, AV block and myocardial depression when amiodarone given with **beta-blockers**; increased myocardial depression when anti-arrhythmics given with **beta-blockers**; increased risk of ventricular arrhythmias when amiodarone given with **sotalol**—avoid concomitant use
 - Calcium-channel Blockers: increased risk of bradycardia, AV block and myocardial depression when amiodarone given with **diltiazem** or **verapamil**
 - Cardiac Glycosides: amiodarone increases plasma concentration of **digoxin** (halve dose of digoxin)

Cyclosporin: amiodarone possibly increases plasma concentration of **cyclosporin**
 - Cobicistat: plasma concentration of amiodarone possibly increased by **cobicistat**—manufacturer of cobicistat advises avoid concomitant use
 - Colchicine: amiodarone possibly increases risk of **colchicine** toxicity
 - Cytotoxics: amiodarone possibly increases the plasma concentration of **afatinib**—manufacturer of afatinib advises separating administration of amiodarone by 6 to 12 hours; possible increased risk of ventricular arrhythmias when amiodarone given with **bosutinib**; possible increased risk of ventricular arrhythmias when amiodarone given with **vandetanib**—avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with **arsenic trioxide**
- Diuretics: increased cardiac toxicity with amiodarone if hypokalaemia occurs with **acetazolamide**, **loop diuretics** or **thiazides and related diuretics**; amiodarone increases plasma concentration of **eplerenone** (reduce dose of eplerenone)
- Fidaxomicin: avoidance of amiodarone advised by manufacturer of **fidaxomicin**
- Fingolimod: possible increased risk of bradycardia when amiodarone given with **fingolimod**
- Grapefruit Juice: plasma concentration of amiodarone increased by **grapefruit juice**
- Ivabradine: increased risk of ventricular arrhythmias when amiodarone given with **ivabradine**
 - Lipid-regulating Drugs: increased risk of myopathy when amiodarone given with **simvastatin** (see Dose under Simvastatin, p. 126)
 - Lithium: manufacturer of amiodarone advises avoid concomitant use with **lithium** (risk of ventricular arrhythmias)
- Orlistat: plasma concentration of amiodarone possibly reduced by **orlistat**
- Pentamidine Isetionate: increased risk of ventricular arrhythmias when amiodarone given with **pentamidine isetionate**—avoid concomitant use
- Thyroid Hormones: for concomitant use of amiodarone and **thyroid hormones** see p. 82
- Ulcer-healing Drugs: plasma concentration of amiodarone increased by **cimetidine**
- Amisulpride** *see* Antipsychotics
- Amitriptyline** *see* Antidepressants, Tricyclic
- Amiodipine** *see* Calcium-channel Blockers
- Amoxicillin** *see* Penicillins
- Amphotericin**
- Note** Close monitoring required with concomitant administration of nephrotoxic drugs or cytotoxics
- Antibacterials: increased risk of nephrotoxicity when amphotericin given with **aminoglycosides** or **polymyxins**; possible increased risk of nephrotoxicity when amphotericin given with **vancomycin**
- Antifungals: amphotericin reduces renal excretion and increases cellular uptake of **flucytosine** (toxicity possibly increased); effects of amphotericin possibly antagonised by **imidazoles** and **triazoles**; plasma

Amphotericin**Antifungals (continued)**

concentration of amphotericin possibly increased by **micafungin**

- Cardiac Glycosides: hypokalaemia caused by amphotericin increases cardiac toxicity with **cardiac glycosides**
- Ciclosporin: increased risk of nephrotoxicity when amphotericin given with **ciclosporin**
- Corticosteroids: increased risk of hypokalaemia when amphotericin given with **corticosteroids**—avoid concomitant use unless corticosteroids needed to control reactions
- Cytotoxics: increased risk of ventricular arrhythmias when amphotericin given with **arsenic trioxide**
- Diuretics: increased risk of hypokalaemia when amphotericin given with **loop diuretics** or **thiazides and related diuretics**
- Pentamidine Isetionate: possible increased risk of nephrotoxicity when amphotericin given with **pentamidine isetionate**
- Sodium Stibogluconate: possible increased risk of arrhythmias when amphotericin given after **sodium stibogluconate**—manufacturer of sodium stibogluconate advises giving 14 days apart
- Tacrolimus: increased risk of nephrotoxicity when amphotericin given with **tacrolimus**

Ampicillin *see* Penicillins**Anabolic Steroids**

- Anticoagulants: anabolic steroids enhance anticoagulant effect of **coumarins** and **phenindione**
- Antidiabetics: anabolic steroids possibly enhance hypoglycaemic effect of **antidiabetics**

Anaesthetics, General

Note *See also* Surgery and Long-term Medication, p. 634

- ACE Inhibitors: enhanced hypotensive effect when general anaesthetics given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when general anaesthetics given with **adrenergic neurone blockers**
- Alpha-blockers: enhanced hypotensive effect when general anaesthetics given with **alpha-blockers**
- Analgesics: metabolism of etomidate inhibited by **fentanyl** (consider reducing dose of etomidate); effects of thiopental possibly enhanced by **aspirin**; effects of intravenous general anaesthetics and volatile liquid general anaesthetics possibly enhanced by **opioid analgesics**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when general anaesthetics given with **angiotensin-II receptor antagonists**
- Antibacterials: increased risk of hepatotoxicity when isoflurane given with **isoniazid**; effects of thiopental enhanced by **sulfonamides**; hypersensitivity-like reactions can occur when general anaesthetics given with **intravenous vancomycin**
- Antidepressants: increased risk of arrhythmias and hypotension when general anaesthetics given with **tricyclics**
- Antipsychotics: enhanced hypotensive effect when general anaesthetics given with **antipsychotics**; effects of thiopental enhanced by **droperidol**
- Anxiolytics and Hypnotics: increased sedative effect when general anaesthetics given with **anxiolytics and hypnotics**
- Beta-blockers: enhanced hypotensive effect when general anaesthetics given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when general anaesthetics or isoflurane given with **calcium-channel blockers**; general anaesthetics enhance hypotensive effect of **verapamil** (also AV delay)
- Clonidine: enhanced hypotensive effect when general anaesthetics given with **clonidine**
- Cytotoxics: nitrous oxide increases antifolate effect of **methotrexate**—avoid concomitant use

Anaesthetics, General (continued)

Diazoxide: enhanced hypotensive effect when general anaesthetics given with **diazoxide**

Diuretics: enhanced hypotensive effect when general anaesthetics given with **diuretics**

- Dopaminergics: increased risk of arrhythmias when volatile liquid general anaesthetics given with **levodopa**
 - Dopaxam: increased risk of arrhythmias when volatile liquid general anaesthetics given with **doxapram** (avoid doxapram for at least 10 minutes after volatile liquid general anaesthetics)
 - Memantine: increased risk of CNS toxicity when ketamine given with **memantine** (manufacturer of memantine advises avoid concomitant use)
 - Methyldopa: enhanced hypotensive effect when general anaesthetics given with **methyldopa**
 - Metoclopramide: effects of thiopental enhanced by **metoclopramide**
 - Moxonidine: enhanced hypotensive effect when general anaesthetics given with **moxonidine**
 - Muscle Relaxants: increased risk of myocardial depression and bradycardia when propofol given with **suxamethonium**; volatile liquid general anaesthetics enhance effects of **non-depolarising muscle relaxants** and **suxamethonium**; ketamine enhances effects of **atracurium**
 - Nitrates: enhanced hypotensive effect when general anaesthetics given with **nitrates**
 - Oxytocin: oxytocic effect possibly reduced, also enhanced hypotensive effect and risk of arrhythmias when volatile liquid general anaesthetics given with **oxytocin**
 - Probencid: effects of thiopental possibly enhanced by **probencid**
 - Sympathomimetics: manufacturer of isoflurane advises avoid concomitant use with **sympathomimetics** (risk of ventricular arrhythmias); increased risk of arrhythmias when volatile liquid general anaesthetics given with **adrenaline (epinephrine)** or **noradrenaline (norepinephrine)**; increased risk of hypertension when volatile liquid general anaesthetics given with **methylphenidate**
 - Theophylline: increased risk of convulsions when ketamine given with **theophylline**
 - Vasodilator Antihypertensives: enhanced hypotensive effect when general anaesthetics given with **hydralazine**, **minoxidil** or **sodium nitropruside**
- Anaesthetics, General (intravenous)** *see* Anaesthetics, General
- Anaesthetics, General (volatile liquids)** *see* Anaesthetics, General
- Anaesthetics, Local** *see* Bupivacaine, Chloroprocaine, Levobupivacaine, Lidocaine, Prilocaine, and Ropivacaine
- Anagrelide**
- Cilostazol: manufacturer of anagrelide advises avoid concomitant use with **cilostazol**
 - Phosphodiesterase Type-3 Inhibitors: manufacturer of anagrelide advises avoid concomitant use with **enoximone** and **milrinone**
- Anakinra**
- Adalimumab: avoid concomitant use of anakinra with **adalimumab**
 - Certolizumab pegol: avoid concomitant use of anakinra with **certolizumab pegol**
 - Etanercept: avoid concomitant use of anakinra with **etanercept**
 - Golimumab: avoid concomitant use of anakinra with **golimumab**
 - Infliximab: avoid concomitant use of anakinra with **infliximab**
 - Vaccines: avoid concomitant use of anakinra with live **vaccines** (*see* p. 604)
- Analgesics** *see* Aspirin, Nefopam, NSAIDs, Opioid Analgesics, and Paracetamol

Angiotensin-II Receptor Antagonists

ACE Inhibitors: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with **ACE inhibitors**

Adrenergic Neurone Blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **adrenergic neurone blockers**

Alcohol: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **alcohol**

Aldesleukin: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **aldesleukin**

- **Aliskiren**: avoid concomitant use of angiotensin-II receptor antagonists with **aliskiren** (see also under Renin inhibitors, BNF section 2.5.5.3); irbesartan possibly reduces plasma concentration of **aliskiren**

Alpha-blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **alpha-blockers**

Anaesthetics, General: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **general anaesthetics**

Analgesics: increased risk of renal impairment when angiotensin-II receptor antagonists given with **NSAIDs**, also hypotensive effect antagonised

Antibacterials: plasma concentration of losartan and its active metabolite reduced by **rifampicin**; possible increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with **trimethoprim**

Anticoagulants: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with **heparins**

Antidepressants: hypotensive effect of angiotensin-II receptor antagonists possibly enhanced by **MAOIs**

Antipsychotics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **antipsychotics**

Anxiolytics and Hypnotics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **anxiolytics and hypnotics**

Beta-blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **beta-blockers**

Calcium-channel Blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **calcium-channel blockers**

- **Ciclosporin**: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with **ciclosporin**

Clonidine: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **clonidine**

Corticosteroids: hypotensive effect of angiotensin-II receptor antagonists antagonised by **corticosteroids**

Diazoxide: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **diazoxide**

- **Diuretics**: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **diuretics**; increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with **potassium-sparing diuretics and aldosterone antagonists**

Dopaminergics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **levodopa**

- **Lithium**: angiotensin-II receptor antagonists reduce excretion of **lithium** (increased plasma concentration)

Methyldopa: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **methyldopa**

Moxisylyte: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **moxisylyte**

Moxonidine: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **moxonidine**

Muscle Relaxants: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **baclofen or tizanidine**

Angiotensin-II Receptor Antagonists (continued)

Nitrates: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **nitrates**

Oestrogens: hypotensive effect of angiotensin-II receptor antagonists antagonised by **oestrogens**

- **Potassium Salts**: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with **potassium salts**

Prostaglandins: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **alprostadil**

Tacrolimus: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with **tacrolimus**

Vasodilator Antihypertensives: enhanced hypotensive effect when angiotensin-II receptor antagonists given with **hydralazine, minoxidil or sodium nitroprusside**

Antacids

Note Antacids should preferably not be taken at the same time as other drugs since they may impair absorption

ACE Inhibitors: antacids possibly reduce absorption of **ACE inhibitors**; antacids reduce absorption of **captopril, enalapril and fosinopril**

Analgesics: antacids possibly reduce absorption of **acemetacin**; alkaline urine due to some antacids increases excretion of **aspirin**

Antibacterials: antacids reduce absorption of **azithromycin, cefaclor, ciprofloxacin, isoniazid, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, rifampicin and tetracyclines**; avoid concomitant use of antacids with **methenamine**; oral magnesium salts (as magnesium trisilicate) reduce absorption of **nitrofurantoin**

Antiepileptics: antacids reduce absorption of **gabapentin and phenytoin**

Antifungals: antacids reduce absorption of **itraconazole**

Antihistamines: antacids reduce absorption of **fexofenadine**

Antimalarials: antacids reduce absorption of **chloroquine and hydroxychloroquine**; oral magnesium salts (as magnesium trisilicate) reduce absorption of **proguanil**

Antipsychotics: antacids reduce absorption of **phenothiazines and sulpiride**

Antivirals: antacids reduce absorption of **atazanavir** (give at least 2 hours before or 1 hour after antacids); aluminium hydroxide possibly reduces absorption of **dolutegravir**—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after aluminium hydroxide; oral magnesium salts possibly reduce absorption of **dolutegravir**—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after oral magnesium salts; antacids reduce absorption of **elvitegravir** (give at least 4 hours apart); antacids possibly reduce absorption of **raltegravir** (give at least 2 hours apart); manufacturer of rilpivirine advises give antacids 2 hours before or 4 hours after **rilpivirine**; antacids reduce absorption of **tipranavir**

Bile Acids: antacids possibly reduce absorption of **bile acids**

Bisphosphonates: antacids reduce absorption of **bisphosphonates**

Cardiac Glycosides: antacids possibly reduce absorption of **digoxin**

Corticosteroids: antacids reduce absorption of **deflazacort**

- **Cytotoxics**: aluminium hydroxide and oral magnesium salts possibly reduce absorption of **estramustine**—manufacturer of estramustine advises avoid concomitant administration; separating administration with antacids by about 12 hours advised by manufacturer of **bosutinib**; antacids possibly reduce

Antacids

- Cytotoxics (*continued*)
 - plasma concentration of **erlotinib**—give antacids at least 4 hours before or 2 hours after erlotinib
- Deferasirox: antacids containing aluminium possibly reduce absorption of **deferasirox** (manufacturer of deferasirox advises avoid concomitant use)
- Deferiprone: antacids containing aluminium possibly reduce absorption of **deferiprone** (manufacturer of deferiprone advises avoid concomitant use)
- Dipyridamole: antacids possibly reduce absorption of **dipyridamole**
- Eltrombopag: antacids reduce absorption of **eltrombopag** (give at least 4 hours apart)
- Iron: oral magnesium salts (as magnesium trisilicate) reduce absorption of **oral iron**
- Lipid-regulating Drugs: antacids reduce absorption of **rosuvastatin**
- Lithium: sodium bicarbonate increases excretion of **lithium** (reduced plasma concentration)
- Mycophenolate: antacids reduce absorption of **mycophenolate**
- Penicillamine: antacids reduce absorption of **penicillamine**
- Polystyrene Sulfonate Resins: risk of intestinal obstruction when aluminium hydroxide given with **polystyrene sulfonate resins**; risk of metabolic alkalosis when oral magnesium salts given with **polystyrene sulfonate resins**
- Sympathomimetics: aluminium hydroxide possibly increases absorption of **pseudoephedrine**
- Thyroid Hormones: antacids possibly reduce absorption of **levothyroxine**
- Ulcer-healing Drugs: antacids possibly reduce absorption of **lansoprazole**
- Ulipristal: avoidance of antacids advised by manufacturer of **high-dose ulipristal** (contraceptive effect of ulipristal possibly reduced)

Antazoline *see* Antihistamines

Anti-arrhythmics *see* Adenosine, Amiodarone, Disopyramide, Dronedronarone, Flecainide, Lidocaine, and Propafenone

Antibacterials *see* individual drugs

Antibiotics (cytotoxic) *see* Bleomycin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, and Mitoxantrone

Anticoagulants *see* Apixaban, Coumarins, Dabigatran, Heparins, Phenindione, and Rivaroxaban

Antidepressants *see* Agomelatine; Antidepressants, SSRI; Antidepressants, Tricyclic; Antidepressants, Tricyclic (related); MAOIs; Mirtazapine; Moclobemide; Reboxetine; St John's Wort; Venlafaxine

Antidepressants, Noradrenaline Re-uptake Inhibitors *see* Reboxetine

Antidepressants, SSRI

Note *see also* Dapoxetine

- Alcohol: sedative effects possibly increased when SSRIs given with **alcohol**
- Anaesthetics, Local: fluvoxamine inhibits metabolism of **ropivacaine**—avoid prolonged administration of ropivacaine
- Analgesics: increased risk of bleeding when SSRIs given with **NSAIDs** or **aspirin**; possible increased serotonergic effects when SSRIs given with **fentanyl**; fluoxetine, fluvoxamine, paroxetine and sertraline possibly increase plasma concentration of **methadone**; increased risk of CNS toxicity when SSRIs given with **tramadol**
- Anti-arrhythmics: manufacturer of citalopram and escitalopram advises avoid concomitant use with **amiodarone** (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with **disopyramide** (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with **anti-arrhythmics** (*continued*)
 - with **dronedronarone** (risk of ventricular arrhythmias); fluoxetine increases plasma concentration of **flecainide**; fluoxetine and paroxetine possibly inhibit metabolism of **propafenone**
- Antibacterials: manufacturer of citalopram and escitalopram advises avoid concomitant use with **intravenous erythromycin** (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with **moxifloxacin** (risk of ventricular arrhythmias); possible increased risk of ventricular arrhythmias when citalopram given with **telithromycin**
- Anticoagulants: SSRIs possibly enhance anticoagulant effect of **coumarins**; possible increased risk of bleeding when SSRIs given with **dabigatran**
- Antidepressants: avoidance of fluvoxamine advised by manufacturer of **reboxetine**; possible increased serotonergic effects when SSRIs given with **duloxetine**; fluvoxamine inhibits metabolism of **duloxetine**—avoid concomitant use; citalopram, escitalopram, fluvoxamine, paroxetine or sertraline should not be started until 2 weeks after stopping **MAOIs**, also MAOIs should not be started until at least 1 week after stopping citalopram, escitalopram, fluvoxamine, paroxetine or sertraline; fluoxetine should not be started until 2 weeks after stopping **MAOIs**, also MAOIs should not be started until at least 5 weeks after stopping fluoxetine; CNS effects of SSRIs increased by **MAOIs** (risk of serious toxicity); increased risk of CNS toxicity when escitalopram given with **moclobemide**, preferably avoid concomitant use; after stopping citalopram, fluvoxamine, paroxetine or sertraline do not start **moclobemide** for at least 1 week; after stopping fluoxetine do not start **moclobemide** for 5 weeks; increased serotonergic effects when SSRIs given with **St John's wort**—avoid concomitant use; fluvoxamine inhibits metabolism of **agomelatine** (increased plasma concentration); possible increased serotonergic effects when fluoxetine or fluvoxamine given with **mirtazapine**; SSRIs increase plasma concentration of some **tricyclics**; manufacturer of citalopram and escitalopram advises avoid concomitant use with **tricyclics** (risk of ventricular arrhythmias)
- Antiepileptics: SSRIs antagonise anticonvulsant effect of **antiepileptics** (convulsive threshold lowered); fluoxetine and fluvoxamine increase plasma concentration of **carbamazepine**; plasma concentration of paroxetine reduced by **phenobarbital** and **phenytoin**; fluoxetine and fluvoxamine increase plasma concentration of **phenytoin**; plasma concentration of sertraline possibly reduced by **phenytoin**, also plasma concentration of phenytoin possibly increased
- Antifungals: plasma concentration of paroxetine possibly increased by **terbinafine**
- Antihistamines: manufacturer of citalopram and escitalopram advises avoid concomitant use with **mizolastine** (risk of ventricular arrhythmias); antidepressant effect of SSRIs possibly antagonised by **cyproheptadine**
- Antimalarials: manufacturer of citalopram and escitalopram advises avoid concomitant use with **antimalarials** (risk of ventricular arrhythmias); avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperazine with arteminol**
- Antimuscarinics: paroxetine increases plasma concentration of **darifenacin** and **procyclidine**
- Antipsychotics: avoidance of fluoxetine, fluvoxamine and sertraline advised by manufacturer of **droperidol** (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with **haloperidol** (risk of ventricular

Antidepressants, SSRI● Antipsychotics (*continued*)

arrhythmias; fluoxetine increases plasma concentration of ●**clozapine**, ●**haloperidol** and **risperidone**; fluvoxamine possibly increases plasma concentration of **asenapine** and **haloperidol**; paroxetine inhibits metabolism of **perphenazine** (reduce dose of perphenazine); fluoxetine and paroxetine possibly increase plasma concentration of ●**aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); plasma concentration of paroxetine possibly increased by **asenapine**; fluvoxamine, paroxetine and sertraline increase plasma concentration of ●**clozapine**; citalopram possibly increases plasma concentration of **clozapine** (increased risk of toxicity); fluvoxamine increases plasma concentration of **olanzapine**; manufacturer of citalopram and escitalopram advises avoid concomitant use with ●**phenothiazines** (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with ●**pimozide** (risk of ventricular arrhythmias); SSRIs possibly increase plasma concentration of ●**pimozide** (increased risk of ventricular arrhythmias—avoid concomitant use); paroxetine possibly increases plasma concentration of **risperidone** (increased risk of toxicity)

● Antivirals: plasma concentration of paroxetine and sertraline possibly reduced by **darunavir**; plasma concentration of paroxetine possibly reduced by **ritonavir**; plasma concentration of SSRIs possibly increased by ●**ritonavir**● Anxiolytics and Hypnotics: fluoxetine increases plasma concentration of **alprazolam**; fluvoxamine increases plasma concentration of some **benzodiazepines**; fluvoxamine increases plasma concentration of ●**melatonin**—avoid concomitant use; sedative effects possibly increased when sertraline given with **zolpidem**

Atomoxetine: possible increased risk of convulsions when antidepressants given with **atomoxetine**; fluoxetine and paroxetine possibly inhibit metabolism of **atomoxetine**

● Beta-blockers: citalopram and escitalopram increase plasma concentration of **metoprolol**; paroxetine possibly increases the plasma concentration of ●**metoprolol**—increased risk of AV block (manufacturer of paroxetine advises avoid concomitant use in cardiac insufficiency); fluvoxamine increases plasma concentration of **propranolol**; manufacturer of escitalopram advises avoid concomitant use with ●**sotalol** (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when citalopram given with ●**sotalol**—avoid concomitant use

Bupropion: plasma concentration of citalopram possibly increased by **bupropion**

Calcium-channel Blockers: fluoxetine possibly inhibits metabolism of **nifedipine** (increased plasma concentration)

● Clopidogrel: fluoxetine and fluvoxamine possibly reduce antiplatelet effect of ●**clopidogrel**● Dapoxetine: possible increased risk of serotonergic effects when SSRIs given with ●**dapoxetine** (manufacturer of dapoxetine advises SSRIs should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping SSRIs)● Dopaminergics: increased risk of CNS toxicity when SSRIs given with ●**rasagiline**; fluvoxamine should not be started until 2 weeks after stopping ●**rasagiline**; fluoxetine should not be started until 2 weeks after stopping ●**rasagiline**, also **rasagiline** should not be started until at least 5 weeks after stopping fluoxetine; increased risk of hypertension and CNS excitation when paroxetine given with ●**selegiline** (selegiline should not be started until 2 weeks after stopping paroxetine, avoid paroxetine for 2 weeks after stopping selegiline); increased risk of hyper-**Antidepressants, SSRI**● Dopaminergics (*continued*)

tension and CNS excitation when fluvoxamine or sertraline given with ●**selegiline** (selegiline should not be started until 1 week after stopping fluvoxamine or sertraline, avoid fluvoxamine or sertraline for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when fluoxetine given with ●**selegiline** (selegiline should not be started until 5 weeks after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline); avoidance of citalopram and escitalopram advised by manufacturer of **selegiline**

Grapefruit Juice: plasma concentration of sertraline possibly increased by **grapefruit juice**

● Hormone Antagonists: fluoxetine and paroxetine possibly inhibit metabolism of ●**tamoxifen** to active metabolite (avoid concomitant use)● 5HT₁-receptor Agonists: increased risk of CNS toxicity when citalopram given with ●**5HT₁ agonists** (manufacturer of citalopram advises avoid concomitant use); fluvoxamine inhibits the metabolism of **frovatriptan**; possible increased serotonergic effects when SSRIs given with **naratriptan**; increased risk of CNS toxicity when citalopram, escitalopram, fluoxetine, fluvoxamine or paroxetine given with ●**sumatriptan**; CNS toxicity reported when sertraline given with **sumatriptan**; fluvoxamine possibly inhibits metabolism of **zolmitriptan** (reduce dose of zolmitriptan)● Lithium: Increased risk of CNS effects when SSRIs given with ●**lithium** (lithium toxicity reported)● Methylthioninium: risk of CNS toxicity when SSRIs given with ●**methylthioninium**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

Metoclopramide: CNS toxicity reported when SSRIs given with **metoclopramide**

● Muscle Relaxants: fluvoxamine increases plasma concentration of ●**tizanidine** (increased risk of toxicity)—avoid concomitant use

Parasympathomimetics: paroxetine increases plasma concentration of **galantamine**

● Pentamidine Isetonate: manufacturer of citalopram and escitalopram advises avoid concomitant use with ●**pentamidine isetonate** (risk of ventricular arrhythmias)● Pifrenidone: fluvoxamine increases plasma concentration of ●**pifrenidone**—manufacturer of pifrenidone advises avoid concomitant use● Pomalidomide: fluvoxamine increases plasma concentration of ●**pomalidomide**

Ranolazine: paroxetine possibly increases plasma concentration of **ranolazine**

Roflumilast: fluvoxamine inhibits the metabolism of **roflumilast**

Sympathomimetics: metabolism of SSRIs possibly inhibited by **methylphenidate**

● Theophylline: fluvoxamine increases plasma concentration of ●**theophylline** (concomitant use should usually be avoided, but where not possible halve theophylline dose and monitor plasma-theophylline concentration)

Ticagrelor: possible increased risk of bleeding when citalopram, paroxetine or sertraline given with **ticagrelor**

Ulcer-healing Drugs: plasma concentration of citalopram, escitalopram and sertraline increased by **cimetidine**; fluvoxamine possibly increases plasma concentration of **lansoprazole**; plasma concentration of escitalopram increased by **omeprazole**

Antidepressants, SSRI (related) see Duloxetine and Venlafaxine

Antidepressants, Tricyclic

- Adrenergic Neurone Blockers: tricyclics antagonise hypotensive effect of **adrenergic neurone blockers**
- Alcohol: increased sedative effect when tricyclics given with **alcohol**
 - Alpha₂-adrenoceptor Stimulants: avoidance of tricyclics advised by manufacturer of **apraclonidine** and **brimonidine**
 - Anaesthetics, General: increased risk of arrhythmias and hypotension when tricyclics given with **general anaesthetics**
 - Analgesics: increased risk of CNS toxicity when tricyclics given with **tramadol**; side-effects possibly increased when tricyclics given with **nefopam**; sedative effects possibly increased when tricyclics given with **opioid analgesics**
 - Anti-arrhythmics: increased risk of ventricular arrhythmias when tricyclics given with **amiodarone**—avoid concomitant use; increased risk of ventricular arrhythmias when tricyclics given with **disopyramide** or **flecainide**; avoidance of tricyclics advised by manufacturer of **dronedarone** (risk of ventricular arrhythmias); increased risk of arrhythmias when tricyclics given with **propafenone**
 - Antibacterials: increased risk of ventricular arrhythmias when tricyclics given with **moxifloxacin**—avoid concomitant use; possible increased risk of ventricular arrhythmias when tricyclics given with **telithromycin**
 - Anticoagulants: tricyclics may enhance or reduce anticoagulant effect of **coumarins**
 - Antidepressants: avoidance of tricyclics advised by manufacturer of **citalopram** and **escitalopram** (risk of ventricular arrhythmias); possible increased serotonergic effects when amitriptyline or clomipramine given with **duloxetine**; increased risk of hypertension and CNS excitation when tricyclics given with **MAOIs**, tricyclics should not be started until 2 weeks after stopping MAOIs (3 weeks if starting clomipramine or imipramine), also MAOIs should not be started for at least 1–2 weeks after stopping tricyclics (3 weeks in the case of clomipramine or imipramine); after stopping tricyclics do not start **moclobemide** for at least 1 week; plasma concentration of some tricyclics increased by **SSRIs**; plasma concentration of amitriptyline reduced by **St John's wort**
 - Antiepileptics: tricyclics antagonise anticonvulsant effect of **antiepileptics** (convulsive threshold lowered); metabolism of tricyclics accelerated by **carbamazepine** (reduced plasma concentration and reduced effect); metabolism of tricyclics possibly accelerated by **phenobarbital** (reduced plasma concentration); plasma concentration of tricyclics possibly reduced by **phenytoin**
 - Antifungals: plasma concentration of amitriptyline and nortriptyline possibly increased by **fluconazole**; plasma concentration of tricyclics possibly increased by **terbinafine**
 - Antihistamines: increased antimuscarinic and sedative effects when tricyclics given with **antihistamines**
 - Antimalarials: avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperazine with artenimol**
 - Antimuscarinics: increased risk of antimuscarinic side-effects when tricyclics given with **antimuscarinics**
 - Antipsychotics: avoidance of tricyclics advised by manufacturer of **droperidol**, **fluphenazine**, **haloperidol**, **sulpiride** and **zuclopenthixol** (risk of ventricular arrhythmias); possible increased antimuscarinic side-effects when tricyclics given with **clozapine**; increased risk of antimuscarinic side-effects when tricyclics given with **phenothiazines**
 - Antivirals: plasma concentration of tricyclics possibly increased by **ritonavir**; increased risk of ventricular

Antidepressants, Tricyclic

- Antivirals (*continued*)
arrhythmias when tricyclics given with **saquinavir**—avoid concomitant use
- Anxiolytics and Hypnotics: increased sedative effect when tricyclics given with **anxiolytics and hypnotics**
- Atomoxetine: increased risk of ventricular arrhythmias when tricyclics given with **atomoxetine**; possible increased risk of convulsions when antidepressants given with **atomoxetine**
- Beta-blockers: plasma concentration of imipramine increased by **labetalol** and **propranolol**; increased risk of ventricular arrhythmias when tricyclics given with **sotalol**
- Bupropion: plasma concentration of tricyclics possibly increased by **bupropion** (possible increased risk of convulsions)
- Calcium-channel Blockers: plasma concentration of tricyclics possibly increased by **diltiazem** and **verapamil**; plasma concentration of imipramine increased by **diltiazem** and **verapamil**
- Cannabis Extract: possible increased risk of hypertension and tachycardia when tricyclics given with **cannabis extract**
- Clonidine: tricyclics antagonise hypotensive effect of **clonidine**, also increased risk of hypertension on clonidine withdrawal
- Cytotoxics: increased risk of ventricular arrhythmias when amitriptyline or clomipramine given with **arsenic trioxide**
- Dapoxetine: possible increased risk of serotonergic effects when tricyclics given with **dapoxetine** (manufacturer of dapoxetine advises tricyclics should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tricyclics)
- Disulfiram: metabolism of tricyclics inhibited by **disulfiram** (increased plasma concentration); concomitant amitriptyline reported to increase **disulfiram** reaction with alcohol
- Diuretics: increased risk of postural hypotension when tricyclics given with **diuretics**
- Dopaminergics: caution with tricyclics advised by manufacturer of **entacapone**; increased risk of CNS toxicity when tricyclics given with **rasagiline**; CNS toxicity reported when tricyclics given with **selegiline**
- Histamine: tricyclics theoretically antagonise effects of **histamine**—manufacturer of histamine advises avoid concomitant use
- Lithium: risk of toxicity when tricyclics given with **lithium**
- Methylthioninium: risk of CNS toxicity when clomipramine given with **methylthioninium**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)
- Moxonidine: tricyclics possibly antagonise hypotensive effect of **moxonidine** (manufacturer of moxonidine advises avoid concomitant use)
- Muscle Relaxants: tricyclics enhance muscle relaxant effect of **baclofen**
- Nicorandil: tricyclics possibly enhance hypotensive effect of **nicorandil**
- Nitrates: tricyclics reduce effects of sublingual tablets of **nitrates** (failure to dissolve under tongue owing to dry mouth)
- Oestrogens: antidepressant effect of tricyclics antagonised by **oestrogens** (but side-effects of tricyclics possibly increased due to increased plasma concentration)
- Pentamidine Isetionate: increased risk of ventricular arrhythmias when tricyclics given with **pentamidine isetionate**

Antidepressants, Tricyclic *(continued)*

Sodium Oxybate: increased risk of side-effects when tricyclics given with **sodium oxybate**

- Sympathomimetics: increased risk of hypertension and arrhythmias when tricyclics given with **adrenaline (epinephrine)** (but local anaesthetics with adrenaline appear to be safe); metabolism of tricyclics possibly inhibited by **methylephedrine**; increased risk of hypertension and arrhythmias when tricyclics given with **noradrenaline (norepinephrine)** or **phenylephrine**

Thyroid Hormones: effects of tricyclics possibly enhanced by **thyroid hormones**; effects of amitriptyline and imipramine enhanced by **thyroid hormones**

Ulcer-healing Drugs: plasma concentration of tricyclics possibly increased by **cimetidine**; metabolism of amitriptyline, doxepin, imipramine and nortriptyline inhibited by **cimetidine** (increased plasma concentration)

Antidepressants, Tricyclic (related)

- Alcohol: increased sedative effect when tricyclic-related antidepressants given with **alcohol**
- Alpha₂-adrenoceptor Stimulants: avoidance of tricyclic-related antidepressants advised by manufacturer of **apraclonidine** and **brimonidine**
- Antibacterials: plasma concentration of trazodone possibly increased by **clarithromycin**
- Anticoagulants: trazodone may enhance or reduce anticoagulant effect of **warfarin**
- Antidepressants: tricyclic-related antidepressants should not be started until 2 weeks after stopping **MAOIs**, also MAOIs should not be started until at least 1–2 weeks after stopping tricyclic-related antidepressants; after stopping tricyclic-related antidepressants do not start **moclobemide** for at least 1 week
- Antiepileptics: tricyclic-related antidepressants possibly antagonise anticonvulsant effect of **antiepileptics** (convulsive threshold lowered); plasma concentration of mianserin and trazodone reduced by **carbamazepine**; metabolism of mianserin accelerated by **phenobarbital** (reduced plasma concentration); plasma concentration of mianserin reduced by **phenytoin**
- Antihistamines: possible increased antimuscarinic and sedative effects when tricyclic-related antidepressants given with **antihistamines**
- Antimalarials: avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperazine with arteminol**
- Antimuscarinics: possible increased antimuscarinic side-effects when tricyclic-related antidepressants given with **antimuscarinics**
- Antivirals: plasma concentration of trazodone increased by **ritonavir** (increased risk of toxicity); increased risk of ventricular arrhythmias when trazodone given with **squinavir**—avoid concomitant use; plasma concentration of trazodone possibly increased by **telaprevir**
- Anxiolytics and Hypnotics: increased sedative effect when tricyclic-related antidepressants given with **anxiolytics and hypnotics**
- Atomoxetine: possible increased risk of convulsions when antidepressants given with **atomoxetine**
- Diazoxide: enhanced hypotensive effect when tricyclic-related antidepressants given with **diazoxide**
- Nitrates: tricyclic-related antidepressants possibly reduce effects of sublingual tablets of **nitrates** (failure to dissolve under tongue owing to dry mouth)
- Vasodilator Antihypertensives: enhanced hypotensive effect when tricyclic-related antidepressants given with **hydralazine** or **sodium nitroprusside**

Antidiabetics

Note Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after lixisenatide injection,

Antidiabetics *(continued)*

or taken with a meal when lixisenatide is not administered, to minimise possible interference with absorption

Note Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after exenatide injection, or taken with a meal when exenatide is not administered, to minimise possible interference with absorption

ACE Inhibitors: hypoglycaemic effect of insulin, metformin and sulfonylureas possibly enhanced by **ACE inhibitors**

Alcohol: hypoglycaemic effect of antidiabetics enhanced by **alcohol**; increased risk of lactic acidosis when metformin given with **alcohol**

Anabolic Steroids: hypoglycaemic effect of antidiabetics possibly enhanced by **anabolic steroids**

- Analgesics: effects of sulfonylureas possibly enhanced by **NSAIDs**; lixisenatide possibly reduces the absorption of **paracetamol** when given 1 to 4 hours before paracetamol
- Anti-arrhythmics: hypoglycaemic effect of gliclazide, insulin and metformin possibly enhanced by **disopyramide**
- Antibacterials: hypoglycaemic effect of acarbose possibly enhanced by **neomycin**, also severity of gastro-intestinal effects increased; effects of repaglinide enhanced by **clarithromycin**; effects of glibenclamide possibly enhanced by **norfloxacin**; plasma concentration of canagliflozin and nateglinide reduced by **rifampicin**; effects of linagliptin possibly reduced by **rifampicin**; hypoglycaemic effect of repaglinide possibly antagonised by **rifampicin**; effects of sulfonylureas enhanced by **chloramphenicol**; metabolism of tolbutamide accelerated by **rifamycins** (reduced effect); metabolism of sulfonylureas possibly accelerated by **rifamycins** (reduced effect); effects of sulfonylureas rarely enhanced by **sulfonamides** and **trimethoprim**; hypoglycaemic effect of sulfonylureas possibly enhanced by **tetracyclines**; hypoglycaemic effect of repaglinide possibly enhanced by **trimethoprim**—manufacturer advises avoid concomitant use
- Anticoagulants: exenatide possibly enhances anticoagulant effect of **warfarin**; hypoglycaemic effect of sulfonylureas possibly enhanced by **coumarins**, also possible changes to anticoagulant effect
- Antidepressants: hypoglycaemic effect of antidiabetics possibly enhanced by **MAOIs**; hypoglycaemic effect of insulin, metformin and sulfonylureas enhanced by **MAOIs**
- Antidiabetics: manufacturer of dapagliflozin advises avoid concomitant use with **pioglitazone**
- Antiepileptics: tolbutamide transiently increases plasma concentration of **phenytoin** (possibility of toxicity); plasma concentration of metformin possibly increased by **topiramate**; plasma concentration of glibenclamide possibly reduced by **topiramate**
- Antifungals: plasma concentration of sulfonylureas increased by **fluconazole** and **micronazole**; hypoglycaemic effect of gliclazide and glipizide enhanced by **micronazole**—avoid concomitant use; hypoglycaemic effect of nateglinide possibly enhanced by **fluconazole**; hypoglycaemic effect of repaglinide possibly enhanced by **itraconazole**; hypoglycaemic effect of glipizide possibly enhanced by **posaconazole**; plasma concentration of sulfonylureas possibly increased by **voriconazole**
- Antihistamines: thrombocyte count depressed when metformin given with **ketotifen** (manufacturer of ketotifen advises avoid concomitant use)
- Antipsychotics: hypoglycaemic effect of sulfonylureas possibly antagonised by **phenothiazines**
- Antivirals: plasma concentration of tolbutamide possibly increased by **ritonavir**
- Appetite: plasma concentration of tolbutamide reduced by **aprepitant**

Antidiabetics (*continued*)

- Beta-blockers: warning signs of hypoglycaemia (such as tremor) with antidiabetics may be masked when given with **beta-blockers**; hypoglycaemic effect of insulin enhanced by **beta-blockers**
- Bosentan: increased risk of hepatotoxicity when glibenclamide given with **bosentan**—avoid concomitant use
- Calcium-channel Blockers: glucose tolerance occasionally impaired when insulin given with **nifedipine**
- Cardiac Glycosides: canagliflozin and sitagliptin increase plasma concentration of **digoxin**; acarbose possibly reduces plasma concentration of **digoxin**
- Ciclosporin: hypoglycaemic effect of repaglinide possibly enhanced by **ciclosporin**
- Corticosteroids: hypoglycaemic effect of antidiabetics antagonised by **corticosteroids**
- Cytotoxics: avoidance of repaglinide advised by manufacturer of **lapatinib**; plasma concentration of metformin possibly increased by **vandetanib** (consider reducing dose of metformin)
- Deferasirox: plasma concentration of repaglinide increased by **deferasirox**
- Diazoxide: hypoglycaemic effect of antidiabetics antagonised by **diazoxide**
- Diuretics: canagliflozin possibly enhances diuretic effect of **diuretics**; manufacturer of canagliflozin advises avoid concomitant use with **loop diuretics**; hypoglycaemic effect of antidiabetics antagonised by **loop diuretics** and **thiazides and related diuretics**; dapagliflozin possibly enhances diuretic effect of **loop diuretics** and **thiazides and related diuretics**
- Hormone Antagonists: requirements for antidiabetics possibly reduced by **lanreotide**, **octreotide** and **pasireotide**
- Leflunomide: hypoglycaemic effect of tolbutamide possibly enhanced by **leflunomide**
- Lipid-regulating Drugs: absorption of glibenclamide and glipizide reduced by **colexvelam**; absorption of glimepiride reduced by **colexvelam**—manufacturer of glimepiride advises give at least 4 hours before colexvelam; hypoglycaemic effect of acarbose possibly enhanced by **colestyramine**; hypoglycaemic effect of nateglinide possibly enhanced by **gemfibrozil**; increased risk of severe hypoglycaemia when repaglinide given with **gemfibrozil**—avoid concomitant use; plasma concentration of glibenclamide possibly increased by **fluvastatin**; manufacturer of canagliflozin advises give at least 1 hour before or 4–6 hours after **bile acid sequestrants**; may be improved glucose tolerance and an additive effect when insulin or sulfonylureas given with **fibrates**
- Oestrogens: hypoglycaemic effect of antidiabetics antagonised by **oestrogens**
- Orlistat: avoidance of acarbose advised by manufacturer of **orlistat**
- Pancreatin: hypoglycaemic effect of acarbose antagonised by **pancreatin**
- Progestogens: hypoglycaemic effect of antidiabetics antagonised by **progestogens**
- Sulfapyrazone: effects of sulfonylureas enhanced by **sulfapyrazone**
- Teriflunomide: plasma concentration of repaglinide increased by **teriflunomide**
- Testosterone: hypoglycaemic effect of antidiabetics possibly enhanced by **testosterone**
- Ulcer-healing Drugs: excretion of metformin reduced by **cimetidine** (increased plasma concentration); hypoglycaemic effect of sulfonylureas enhanced by **cimetidine**
- Antiepileptics** *see* Carbamazepine, Eslicarbazepine, Ethosuximide, Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Perampanel, Phenobarbital, Phenytoin, Pregabalin, Retigabine, Rufinamide, Stiripentol, Tiagabine, Topiramate, Valproate, Vigabatrin, and Zonisamide

Antifungals *see* Amphotericin; Antifungals, Imidazole; Antifungals, Triazole; Caspofungin; Flucytosine; Griseofulvin; Micafungin; Terbinafine

Antifungals, Imidazole

- Anticoagulants: miconazole enhances anticoagulant effect of **coumarins** (miconazole oral gel and possibly vaginal and topical formulations absorbed)
 - Antidepressants: avoidance of imidazoles advised by manufacturer of **erboxetine**
 - Antidiabetics: miconazole enhances hypoglycaemic effect of **glipizide** and **glipizide**—avoid concomitant use; miconazole increases plasma concentration of **sulfonylureas**
 - Antiepileptics: miconazole possibly increases plasma concentration of **carbamazepine**; miconazole enhances anticonvulsant effect of **phenytoin** (plasma concentration of phenytoin increased)
- Antifungals: imidazoles possibly antagonise effects of **amphotericin**
- Antihistamines: imidazoles possibly inhibit metabolism of **mizolastine** (avoid concomitant use)
 - Antimalarials: avoidance of imidazoles advised by manufacturer of **piperaquine with artemisinin** (possible risk of ventricular arrhythmias); avoidance of imidazoles advised by manufacturer of **artemether with lumefantrine**
 - Antipsychotics: increased risk of ventricular arrhythmias when imidazoles given with **pimozide**—avoid concomitant use; imidazoles possibly increase plasma concentration of **quetiapine**—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: imidazoles possibly increase plasma concentration of **saquinavir**
- Ciclosporin: miconazole possibly inhibits metabolism of **ciclosporin** (increased plasma concentration)
 - Ergot Alkaloids: increased risk of ergotism when imidazoles given with **ergotamine**—avoid concomitant use
 - Lipid-regulating Drugs: possible increased risk of myopathy when imidazoles given with **atorvastatin**; possible increased risk of myopathy when miconazole given with **simvastatin**
- Oestrogens: anecdotal reports of contraceptive failure when imidazoles given with **oestrogens**
- Sirolimus: miconazole increases plasma concentration of **sirolimus**
 - Tacrolimus: miconazole *oral gel* possibly increases plasma concentration of **tacrolimus**
- Antifungals, Polyene** *see* Amphotericin
- Antifungals, Triazole**
- Note** In general, fluconazole interactions relate to multiple-dose treatment
- Aliskiren: itraconazole increases plasma concentration of **aliskiren**—avoid concomitant use
 - Analgesics: fluconazole increases plasma concentration of **celecoxib** (halve dose of celecoxib); voriconazole increases plasma concentration of **diclofenac**, **ibuprofen** and **oxycodone**; fluconazole increases plasma concentration of **flurbiprofen**, **ibuprofen** and **methadone**; fluconazole increases plasma concentration of **parecoxib** (reduce dose of parecoxib); voriconazole increases plasma concentration of **alfentanil** and **methadone** (consider reducing dose of alfentanil and methadone); fluconazole inhibits metabolism of **alfentanil** (risk of prolonged or delayed respiratory depression); itraconazole possibly inhibits metabolism of **alfentanil**; triazoles possibly increase plasma concentration of **fenitoin**; itraconazole possibly increases plasma concentration of **methadone** (increased risk of ventricular arrhythmias); itraconazole increases plasma concentration of **oxycodone**
- Antacids: absorption of itraconazole reduced by **antacids**
- Anti-arrhythmics: manufacturer of itraconazole advises avoid concomitant use with **disopyramide**; avoid-

Antifungals, Triazole

- Anti-arrhythmics (*continued*)
 - avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of ●**dronedarone**
- Antibacterials: plasma concentration of itraconazole increased by ●**clarithromycin**; manufacturer of fluconazole advises avoid concomitant use with ●**erythromycin**; triazoles possibly increase plasma concentration of ●**rifabutin** (increased risk of uveitis—reduce rifabutin dose); posaconazole increases plasma concentration of ●**rifabutin** (also plasma concentration of posaconazole reduced); voriconazole increases plasma concentration of ●**rifabutin**, also rifabutin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for rifabutin toxicity); fluconazole increases plasma concentration of ●**rifabutin** (increased risk of uveitis—reduce rifabutin dose); plasma concentration of itraconazole reduced by ●**rifabutin** and ●**rifampicin**—manufacturer of itraconazole advises avoid concomitant use; plasma concentration of posaconazole reduced by ●**rifampicin**; plasma concentration of voriconazole reduced by ●**rifampicin**—avoid concomitant use; metabolism of fluconazole accelerated by ●**rifampicin** (reduced plasma concentration)
- Anticoagulants: avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of ●**apixaban**; fluconazole, itraconazole and voriconazole enhance anticoagulant effect of ●**coumarins**; avoidance of itraconazole advised by manufacturer of ●**dabigatran** and ●**rivaroxaban**; avoidance of posaconazole and voriconazole advised by manufacturer of ●**rivaroxaban**
- Antidepressants: avoidance of triazoles advised by manufacturer of ●**reboxetine**; fluconazole possibly increases plasma concentration of ●**amitriptyline** and ●**nortriptyline**; plasma concentration of voriconazole reduced by ●**St John's wort**—avoid concomitant use
- Antidiabetics: posaconazole possibly enhances hypoglycaemic effect of ●**glipizide**; fluconazole possibly enhances hypoglycaemic effect of ●**nateglinide**; itraconazole possibly enhances hypoglycaemic effect of ●**repaglinide**; voriconazole possibly increases plasma concentration of ●**sulfonylureas**; fluconazole increases plasma concentration of ●**sulfonylureas**
- Antiepileptics: fluconazole possibly increases plasma concentration of ●**carbamazepine**; plasma concentration of voriconazole possibly reduced by ●**carbamazepine** and ●**phenobarbital**—avoid concomitant use; plasma concentration of itraconazole and posaconazole possibly reduced by ●**carbamazepine**; plasma concentration of itraconazole and posaconazole possibly reduced by ●**phenobarbital**; plasma concentration of posaconazole reduced by ●**phenytoin**; plasma concentration of itraconazole reduced by ●**phenytoin**—avoid concomitant use; fluconazole increases plasma concentration of ●**phenytoin** (consider reducing dose of phenytoin); voriconazole increases plasma concentration of ●**phenytoin**, also phenytoin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for phenytoin toxicity)

Antifungals: triazoles possibly antagonise effects of ●**amphotericin**; monitoring for increased voriconazole side effects advised by manufacturer of ●**fluconazole** if voriconazole given after fluconazole; plasma concentration of itraconazole increased by ●**miconazole** (consider reducing dose of itraconazole); plasma concentration of fluconazole increased by ●**terbinafine**

- Antihistamines: itraconazole inhibits metabolism of ●**mizolastine**—avoid concomitant use
- Antimalarials: avoidance of triazoles advised by manufacturer of ●**piperazine with arteminol** (possible

Antifungals, Triazole

- Antimalarials (*continued*)
 - risk of ventricular arrhythmias; avoidance of triazoles advised by manufacturer of ●**artemether with lumefantrine**
- Antimuscarinics: avoidance of itraconazole advised by manufacturer of ●**darifenacin** and ●**tolterodine**; manufacturer of fesoterodine advises dose reduction when itraconazole given with ●**fesoterodine**—consult fesoterodine product literature; itraconazole possibly increases plasma concentration of ●**solifenacin**—see Dose under Solifenacin, BNF section 7.4.2
- Antipsychotics: itraconazole possibly increases plasma concentration of ●**haloperidol**; itraconazole possibly increases plasma concentration of ●**aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); increased risk of ventricular arrhythmias when triazoles given with ●**pimozide**—avoid concomitant use; triazoles possibly increase plasma concentration of ●**quetiapine**—manufacturer of quetiapine advises avoid concomitant use; itraconazole possibly increases side-effects of ●**risperidone**
- Antivirals: posaconazole increases plasma concentration of ●**atazanavir**; plasma concentration of voriconazole increased or decreased by ●**atazanavir** and plasma concentration of atazanavir also reduced; plasma concentration of itraconazole and posaconazole reduced by ●**efavirenz**; plasma concentration of voriconazole reduced by ●**efavirenz**, also plasma concentration of efavirenz increased (increase voriconazole dose and reduce efavirenz dose); plasma concentration of both drugs may increase when itraconazole given with ●**fosamprenavir**; plasma concentration of posaconazole possibly reduced by ●**fosamprenavir**; itraconazole increases plasma concentration of ●**indinavir** (consider reducing dose of indinavir); plasma concentration of itraconazole possibly reduced by ●**nevirapine**—consider increasing dose of itraconazole; fluconazole increases plasma concentration of ●**nevirapine**, ●**ritonavir** and ●**tipranavir**; combination of itraconazole with ●**ritonavir** may increase plasma concentration of either drug (or both); plasma concentration of voriconazole reduced by ●**ritonavir**—avoid concomitant use; triazoles possibly increase plasma concentration of ●**saquinavir**; plasma concentration of voriconazole possibly affected by ●**telaprevir** (possible increased risk of ventricular arrhythmias); plasma concentration of posaconazole possibly increased by ●**telaprevir** (increased risk of ventricular arrhythmias); plasma concentration of itraconazole possibly increased by ●**telaprevir**; fluconazole increases plasma concentration of ●**zidovudine** (increased risk of toxicity)
- Anxiolytics and Hypnotics: itraconazole increases plasma concentration of ●**alprazolam**; fluconazole and voriconazole increase plasma concentration of ●**diazepam** (risk of prolonged sedation); fluconazole, itraconazole, posaconazole and voriconazole increase plasma concentration of ●**midazolam** (risk of prolonged sedation); itraconazole increases plasma concentration of ●**buspirone** (reduce dose of buspirone)
- Bosentan: fluconazole possibly increases plasma concentration of ●**bosentan**—avoid concomitant use; itraconazole possibly increases plasma concentration of ●**bosentan**
- Calcium-channel Blockers: negative inotropic effect possibly increased when itraconazole given with ●**calcium-channel blockers**; itraconazole inhibits metabolism of ●**felodipine** (increased plasma concentration); avoidance of itraconazole advised by manufacturer of ●**lercanidipine**; itraconazole possibly inhibits metabolism of ●**dihydropyridines** (increased plasma concentration)

Antifungals, Triazole (*continued*)

- Cardiac Glycosides: itraconazole increases plasma concentration of **digoxin**
- Ciclosporin: fluconazole, itraconazole, posaconazole and voriconazole inhibit metabolism of **ciclosporin** (increased plasma concentration)
- Cilostazol: itraconazole possibly increases plasma concentration of **cilostazol** (see Dose under Cilostazol, BNF section 2.6.4)
- Clopidogrel: fluconazole, itraconazole and voriconazole possibly reduce antiplatelet effect of **clopidogrel**
- Cobicistat: plasma concentration of itraconazole possibly increased by **cobicistat**—manufacturer of cobicistat advises reduce dose of itraconazole
- Colchicine: itraconazole possibly increases risk of **colchicine** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: itraconazole possibly inhibits metabolism of **corticosteroids** and **methylprednisolone**; itraconazole increases the plasma concentration of **inhaled** and **oral** (and possibly also **intranasal** and **rectal**) **budesonide**; itraconazole increases plasma concentration of **inhaled fluticasone**
- Cytotoxics: itraconazole inhibits metabolism of **busulfan** (increased risk of toxicity); fluconazole and itraconazole possibly increase side-effects of **cyclophosphamide**; itraconazole possibly increases the plasma concentration of **afatinib**—manufacturer of afatinib advises separating administration of itraconazole by 6 to 12 hours; itraconazole possibly increases plasma concentration of **axitinib** (reduce dose of axitinib—consult axitinib product literature); fluconazole, itraconazole, posaconazole and voriconazole possibly increase the plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; itraconazole and voriconazole possibly increase plasma concentration of **crizotinib**—manufacturer of crizotinib advises avoid concomitant use; itraconazole, posaconazole and voriconazole possibly increase plasma concentration of **everolimus**—manufacturer of everolimus advises avoid concomitant use; itraconazole increases plasma concentration of **gefitinib**; avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of **lapatinib**; avoidance of voriconazole advised by manufacturer of **nilotinib**; itraconazole and voriconazole possibly increase plasma concentration of **pazopanib** (reduce dose of pazopanib); manufacturer of ruxitinib advises dose reduction when fluconazole, itraconazole, posaconazole and voriconazole given with **ruxolitinib**—consult ruxolitinib product literature; avoidance of itraconazole advised by manufacturer of **temsirolimus** (plasma concentration of temsirolimus possibly increased); itraconazole and voriconazole possibly increase the plasma concentration of **cabazitaxel**—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel; increased risk of toxicity when itraconazole given with **irinotecan**—avoid concomitant use; posaconazole possibly inhibits metabolism of **vinblastine** and **vincristine** (increased risk of neurotoxicity); itraconazole possibly increases risk of **vinblastine**, **vindesine**, **vinflunine** and **vinorelbine** toxicity; itraconazole increases risk of **vincristine** toxicity
- Dapoxetine: manufacturer of dapoxetine advises dose reduction when fluconazole given with **dapoxetine** (see Dose under Dapoxetine, BNF section 7.4.6); avoidance of itraconazole advised by manufacturer of **dapoxetine** (increased risk of toxicity)
- Diuretics: fluconazole increases plasma concentration of **eplerenone** (reduce dose of eplerenone); itraconazole increases plasma concentration of **eplerenone**

Antifungals, Triazole

- Diuretics (*continued*)
none—avoid concomitant use; plasma concentration of fluconazole increased by **hydrochlorothiazide**
- Ergot Alkaloids: manufacturer of itraconazole advises avoid concomitant use with **ergometrine** (increased risk of ergotism); increased risk of ergotism when triazoles given with **ergotamine**—avoid concomitant use
- 5HT₂-receptor Agonists: itraconazole increases plasma concentration of **eletriptan** (risk of toxicity)—avoid concomitant use
- Ivabradine: fluconazole increases plasma concentration of **ivabradine**—reduce initial dose of ivabradine; itraconazole possibly increases plasma concentration of **ivabradine**—avoid concomitant use
- Ivacaftor: itraconazole, posaconazole and voriconazole possibly increase plasma concentration of **ivacaftor** (see Dose under Ivacaftor, p. 165); fluconazole increases plasma concentration of **ivacaftor** (see Dose under Ivacaftor, p. 165)
- Lenalidomide: itraconazole possibly increases plasma concentration of **lenalidomide** (increased risk of toxicity)
- Leukotriene Receptor Antagonists: fluconazole increases plasma concentration of **zafirlukast**
- Lipid-regulating Drugs: increased risk of myopathy when itraconazole, posaconazole or voriconazole given with **atorvastatin**; possible increased risk of myopathy when fluconazole given with **atorvastatin** or **simvastatin**; fluconazole increases plasma concentration of **fluvastatin**—possible increased risk of myopathy; increased risk of myopathy when itraconazole or posaconazole given with **simvastatin** (avoid concomitant use); increased risk of myopathy when voriconazole given with **simvastatin**; avoidance of triazoles advised by manufacturer of **lomitapide** (plasma concentration of lomitapide possibly increased)
- Mirabegron: when given with itraconazole avoid or reduce dose of **mirabegron** in hepatic or renal impairment—see Mirabegron, BNF section 7.4.2
- Oestrogens: plasma concentration of voriconazole increased by **oestrogens**
- Progestogens: plasma concentration of voriconazole possibly increased by **progestogens**
- Ranolazine: itraconazole, posaconazole and voriconazole possibly increase plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use
- Retinoids: fluconazole and voriconazole possibly increase risk of **retinoin** toxicity
- Sildenafil: itraconazole increases plasma concentration of **sildenafil**—reduce initial dose of sildenafil
- Sirolimus: fluconazole and posaconazole possibly increase plasma concentration of **sirolimus**; itraconazole and voriconazole increase plasma concentration of **sirolimus**—avoid concomitant use
- Tacrolimus: fluconazole, itraconazole, posaconazole and voriconazole increase plasma concentration of **tacrolimus** (consider reducing dose of tacrolimus)
- Tadalafil: itraconazole possibly increases plasma concentration of **tadalafil**
- Theophylline: fluconazole possibly increases plasma concentration of **theophylline**
- Ulcer-healing Drugs: plasma concentration of posaconazole reduced by **cimetidine**; voriconazole possibly increases plasma concentration of **esomeprazole**; voriconazole increases plasma concentration of **omeprazole** (consider reducing dose of omeprazole); absorption of itraconazole reduced by **histamine H₂-antagonists** and **proton pump inhibitors**; manufacturer of posaconazole advises avoid concomitant use with **histamine H₂-antagonists** and **pro-**

Antifungals, Triazole

- Ulcer-healing Drugs (*continued*)
ton pump inhibitors (plasma concentration of posaconazole possibly reduced)
 Ulipristal: avoidance of itraconazole advised by manufacturer of **ulipristal**
- Vardenafil: itraconazole possibly increases plasma concentration of ●**vardenafil**—avoid concomitant use

Antihistamines

- Note** Sedative interactions apply to a lesser extent to the non-sedating antihistamines. Interactions do not generally apply to antihistamines used for topical action (including inhalation)
- Alcohol:** increased sedative effect when antihistamines given with **alcohol** (possibly less effect with non-sedating antihistamines)
- Analgesics: sedative effects possibly increased when sedating antihistamines given with ●**opioid analgesics**
 - Antacids: absorption of fexofenadine reduced by **antacids**
 - Anti-arrhythmics: increased risk of ventricular arrhythmias when mizolastine given with ●**amiodarone**, ●**disopyramide** or ●**flecainide**—avoid concomitant use; manufacturer of mizolastine advises avoid concomitant use with **propafenone** (possible risk of ventricular arrhythmias)
 - Antibacterials: plasma concentration of rupatadine increased by **erythromycin**; manufacturer of loratadine advises plasma concentration possibly increased by **erythromycin**; metabolism of mizolastine inhibited by ●**erythromycin**—avoid concomitant use; increased risk of ventricular arrhythmias when mizolastine given with ●**moxifloxacin**—avoid concomitant use; effects of fexofenadine possibly reduced by **rifampicin**; metabolism of mizolastine possibly inhibited by ●**macrolides** (avoid concomitant use)
 - Antidepressants: avoidance of mizolastine advised by manufacturer of ●**citalopram** and ●**escitalopram** (risk of ventricular arrhythmias); manufacturer of promethazine advises avoid for 2 weeks after stopping **MAOIs**; manufacturer of hydroxyzine advises avoid concomitant use with **MAOIs**; increased antimuscarinic and sedative effects when antihistamines given with **MAOIs** or **tricyclics**; cyproheptadine possibly antagonises antidepressant effect of **SSRIs**; possible increased antimuscarinic and sedative effects when antihistamines given with **tricyclic-related antidepressants**
 - Antidiabetics: thrombocyte count depressed when ketotifen given with **metformin** (manufacturer of ketotifen advises avoid concomitant use)
 - Antifungals: metabolism of mizolastine inhibited by ●**itraconazole**—avoid concomitant use; metabolism of mizolastine possibly inhibited by ●**imidazoles** (avoid concomitant use)
 - Antimalarials: avoidance of mizolastine advised by manufacturer of ●**piperquine with artemimol** (possible risk of ventricular arrhythmias)
 - Antimuscarinics: increased risk of antimuscarinic side-effects when antihistamines given with **antimuscarinics**
 - Antivirals: plasma concentration of chlorphenamine possibly increased by **lopinavir**; plasma concentration of non-sedating antihistamines possibly increased by **ritonavir**; increased risk of ventricular arrhythmias when mizolastine given with ●**sacquinavir**—avoid concomitant use
 - Anxiolytics and Hypnotics: increased sedative effect when antihistamines given with **anxiolytics and hypnotics**
 - Beta-blockers: increased risk of ventricular arrhythmias when mizolastine given with ●**sotalol**—avoid concomitant use

Antihistamines (*continued*)

- Betahistine: antihistamines theoretically antagonise effect of **betahistine**
- Cytotoxics: possible increased risk of ventricular arrhythmias when mizolastine given with ●**vandetanib**—avoid concomitant use
 - Grapefruit Juice: plasma concentration of bilastine reduced by **grapefruit juice**; plasma concentration of rupatadine increased by ●**grapefruit juice**—avoid concomitant use
- Histamine: antihistamines theoretically antagonise effects of **histamine**—manufacturer of histamine advises avoid concomitant use
- Ulcer-healing Drugs: manufacturer of loratadine advises plasma concentration possibly increased by **cimetidine**; plasma concentration of hydroxyzine increased by **cimetidine**
- Ulipristal: manufacturer of ulipristal advises give fexofenadine at least 1.5 hours before or after **ulipristal**
- Antihistamines, Non-sedating** *see* Antihistamines
- Antihistamines, Sedating** *see* Antihistamines
- Antimalarials** *see* Artemether with Lumefantrine, Chloroquine and Hydroxychloroquine, Mefloquine, Piperquine with Artemimol, Primaquine, Proguanil, Pyrimethamine, and Quinine
- Antimetabolites** *see* Cladribine, Cytarabine, Decitabine, Fludarabine, Fluorouracil, Gemcitabine, Mercaptopurine, Methotrexate, Pemetrexed, Raltitrexed, and Tioguanine

Antimuscarinics

- Note** Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urine retention, and constipation; concomitant use can also lead to confusion in the elderly. Interactions do not generally apply to antimuscarinics used by inhalation
- Alcohol:** increased sedative effect when hyoscine given with **alcohol**
- Analgesics: possible increased risk of antimuscarinic side-effects when antimuscarinics given with **codeine**; increased risk of antimuscarinic side-effects when antimuscarinics given with **nefopam**
- Anti-arrhythmics: increased risk of ventricular arrhythmias when tolterodine given with ●**amiodarone**, ●**disopyramide** or ●**flecainide**; increased risk of antimuscarinic side-effects when antimuscarinics given with **disopyramide**
- Antibacterials: manufacturer of fesoterodine advises dose reduction when fesoterodine given with **clarithromycin** and **telithromycin**—consult fesoterodine product literature; manufacturer of tolterodine advises avoid concomitant use with **clarithromycin** and **erythromycin**; plasma concentration of darifenacin possibly increased by **erythromycin**; plasma concentration of active metabolite of fesoterodine reduced by **rifampicin**
- Antidepressants: plasma concentration of darifenacin and pyridostigmine increased by **paroxetine**; increased risk of antimuscarinic side-effects when antimuscarinics given with **MAOIs** or **tricyclics**; possible increased antimuscarinic side-effects when antimuscarinics given with **tricyclic-related antidepressants**
- Antifungals: manufacturer of fesoterodine advises dose reduction when fesoterodine given with **itraconazole**—consult fesoterodine product literature; manufacturer of darifenacin and tolterodine advises avoid concomitant use with **itraconazole**; plasma concentration of solifenacin possibly increased by ●**itraconazole**—*see* Dose under Solifenacin, BNFS section 7.4.2
- Antihistamines: increased risk of antimuscarinic side-effects when antimuscarinics given with **antihistamines**
- Antipsychotics: antimuscarinics possibly reduce effects of **haloperidol**; increased risk of antimuscarinic side-effects when antimuscarinics given

Antimuscarinics

Antipsychotics (*continued*)

with **clozapine**; antimuscarinics reduce plasma concentration of **phenothiazines**, but risk of antimuscarinic side-effects increased

- Antivirals: manufacturer of fosetorodine advises dose reduction when fosetorodine given with **atazanavir**, **indinavir**, **ritonavir** and **saquinavir**—consult fosetorodine product literature; manufacturer of darifenacin advises avoid concomitant use with **atazanavir**, **fosamprenavir**, **indinavir**, **lopinavir**, **ritonavir**, **saquinavir** and **tipranavir**; manufacturer of tolterodine advises avoid concomitant use with **fosamprenavir**, **indinavir**, **lopinavir**, **ritonavir** and **saquinavir**; plasma concentration of solifenacin possibly increased by **●ritonavir**—see Dose under Solifenacin, BNF section 7.4.2
- Beta-blockers: increased risk of ventricular arrhythmias when tolterodine given with **●sotalol**
- Calcium-channel Blockers: plasma concentration of solifenacin increased by **verapamil**; manufacturer of darifenacin advises avoid concomitant use with **verapamil**
- Cardiac Glycosides: darifenacin possibly increases plasma concentration of **digoxin**
- Ciclosporin: manufacturer of darifenacin advises avoid concomitant use with **ciclosporin**
- Domperidone: antimuscarinics antagonise effects of **domperidone** on gastro-intestinal activity
- Dopaminergics: antimuscarinics possibly reduce absorption of **levodopa**
- Hormone Antagonists: possible increased risk of bradycardia when ipratropium or oxybutynin given with **pasireotide**
- Memantine: effects of antimuscarinics possibly enhanced by **memantine**
- Metoclopramide: antimuscarinics antagonise effects of **metoclopramide** on gastro-intestinal activity
- Nitrates: antimuscarinics possibly reduce effects of sublingual tablets of **nitrates** (failure to dissolve under tongue owing to dry mouth)
- Parasympathomimetics: antimuscarinics antagonise effects of **parasympathomimetics**

Antipsychotics

Note Increased risk of toxicity with myelosuppressive drugs

Note Avoid concomitant use of clozapine with drugs that have a substantial potential for causing agranulocytosis

ACE Inhibitors: enhanced hypotensive effect when antipsychotics given with **ACE inhibitors**

Adrenergic Neurone Blockers: enhanced hypotensive effect when phenothiazines given with **adrenergic neurone blockers**; higher doses of chlorpromazine antagonise hypotensive effect of **adrenergic neurone blockers**; haloperidol antagonises hypotensive effect of **adrenergic neurone blockers**

Adsorbents: absorption of phenothiazines possibly reduced by **kaolin**

Alcohol: increased sedative effect when antipsychotics given with **alcohol**

Alpha-blockers: enhanced hypotensive effect when antipsychotics given with **alpha-blockers**

- Anaesthetics, General: droperidol enhances effects of **thiopental**; enhanced hypotensive effect when antipsychotics given with **●general anaesthetics**
- Analgesics: possible severe drowsiness when haloperidol given with **acemetacin** or **indometacin**; increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with **●methadone**; increased risk of ventricular arrhythmias when amisulpride given with **●methadone**—avoid concomitant use; increased risk of convulsions when antipsychotics given with **tramadol**; enhanced hypotensive and sedative effects when antipsychotics given with **opioid analgesics**

Antipsychotics (*continued*)

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when antipsychotics given with **angiotensin-II receptor antagonists**

Antacids: absorption of phenothiazines and sulpiride reduced by **antacids**

- Anti-arrhythmics: increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with **●anti-arrhythmics** that prolong the QT interval; increased risk of ventricular arrhythmias when amisulpride, droperidol, haloperidol, phenothiazines, pimozide or zuclopenthixol given with **●amiodarone**—avoid concomitant use; increased risk of ventricular arrhythmias when benperidol given with **●amiodarone**—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when sulpiride given with **●amiodarone** or **●disopyramide**; increased risk of ventricular arrhythmias when amisulpride, droperidol, pimozide or zuclopenthixol given with **●disopyramide**—avoid concomitant use; possible increased risk of ventricular arrhythmias when haloperidol given with **●disopyramide**—avoid concomitant use; increased risk of ventricular arrhythmias when phenothiazines given with **●disopyramide**; avoidance of phenothiazines advised by manufacturer of **●dronedrone** (risk of ventricular arrhythmias); increased risk of arrhythmias when clozapine given with **●lecainide**
- Antibacterials: increased risk of ventricular arrhythmias when pimozide given with **●clarithromycin**, **●moxifloxacin** or **●telithromycin**—avoid concomitant use; plasma concentration of quetiapine possibly increased by **●clarithromycin**—manufacturer of quetiapine advises avoid concomitant use; increased risk of ventricular arrhythmias when amisulpride given with **●erythromycin**—avoid concomitant use; plasma concentration of clozapine possibly increased by **●erythromycin** (possible increased risk of convulsions); possible increased risk of ventricular arrhythmias when pimozide given with **●erythromycin**—avoid concomitant use; plasma concentration of quetiapine increased by **●erythromycin**—manufacturer of quetiapine advises avoid concomitant use; increased risk of ventricular arrhythmias when sulpiride given with **parenteral ●erythromycin**; increased risk of ventricular arrhythmias when zuclopenthixol given with **parenteral ●erythromycin**—avoid concomitant use; plasma concentration of clozapine increased by **ciprofloxacin**; plasma concentration of olanzapine possibly increased by **ciprofloxacin**; increased risk of ventricular arrhythmias when droperidol, haloperidol, phenothiazines or zuclopenthixol given with **●moxifloxacin**—avoid concomitant use; increased risk of ventricular arrhythmias when benperidol given with **●moxifloxacin**—manufacturer of benperidol advises avoid concomitant use; plasma concentration of aripiprazole possibly reduced by **●rifabutin** and **●rifampicin** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); plasma concentration of clozapine possibly reduced by **●rifampicin**; metabolism of haloperidol accelerated by **●rifampicin** (reduced plasma concentration); avoid concomitant use of clozapine with **●chloramphenicol** or **●sulfonamides** (increased risk of agranulocytosis); manufacturer of droperidol advises avoid concomitant use with **●macrolides** (risk of ventricular arrhythmias); plasma concentration of quetiapine possibly increased by **telithromycin**; possible increased risk of ventricular arrhythmias when chlorpromazine given with **●telithromycin**
- Antidepressants: plasma concentration of clozapine possibly increased by **citalopram** (increased risk of toxicity); avoidance of haloperidol, phenothiazines

Antipsychotics● Antidepressants (*continued*)

and pimozone advised by manufacturer of ●**citalopram** (risk of ventricular arrhythmias); avoidance of haloperidol, phenothiazines and pimozone advised by manufacturer of ●**escitalopram** (risk of ventricular arrhythmias); plasma concentration of aripiprazole possibly increased by ●**fluoxetine** and ●**paroxetine** (reduce dose of aripiprazole—consult aripiprazole product literature); plasma concentration of clozapine, haloperidol and risperidone increased by ●**fluoxetine**; manufacturer of droperidol advises avoid concomitant use with ●**fluoxetine**, ●**fluvoxamine**, ●**sertraline** and ●**tricyclics** (risk of ventricular arrhythmias); plasma concentration of asenapine and haloperidol possibly increased by ●**fluvoxamine**; plasma concentration of clozapine and olanzapine increased by ●**fluvoxamine**; asenapine possibly increases plasma concentration of ●**paroxetine**; plasma concentration of clozapine increased by ●**paroxetine** and ●**sertraline**; plasma concentration of risperidone possibly increased by ●**paroxetine** (increased risk of toxicity); metabolism of perphenazine inhibited by ●**paroxetine** (reduce dose of perphenazine); plasma concentration of haloperidol increased by ●**venlafaxine**; clozapine possibly increases CNS effects of ●**MAOIs**; plasma concentration of pimozone possibly increased by ●**SSRIs** (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of aripiprazole possibly reduced by ●**St John's wort** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); manufacturer of fluphenazine, haloperidol, sulpiride and zuclopenthixol advises avoid concomitant use with ●**tricyclics** (risk of ventricular arrhythmias); increased risk of antimuscarinic side-effects when phenothiazines given with ●**tricyclics**; possible increased antimuscarinic side-effects when clozapine given with ●**tricyclics**

Antidiabetics: phenothiazines possibly antagonise hypoglycaemic effect of ●**sulfonylureas**

- Antiepileptics: antipsychotics antagonise anticonvulsant effect of ●**antiepileptics** (convulsive threshold lowered); plasma concentration of paliperidone reduced by ●**carbamazepine**; metabolism of haloperidol, olanzapine, quetiapine and risperidone accelerated by ●**carbamazepine** (reduced plasma concentration); metabolism of clozapine accelerated by ●**carbamazepine** (reduced plasma concentration), also avoid concomitant use of drugs with substantial potential for causing agranulocytosis; plasma concentration of aripiprazole reduced by ●**carbamazepine** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); plasma concentration of clozapine possibly reduced by ●**phenobarbital**; plasma concentration of aripiprazole possibly reduced by ●**phenobarbital** and ●**phenytoin** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); metabolism of haloperidol accelerated by ●**phenobarbital** (reduced plasma concentration); plasma concentration of both drugs reduced when chlorpromazine given with ●**phenobarbital**; plasma concentration of haloperidol reduced by ●**phenytoin**; chlorpromazine possibly increases or decreases plasma concentration of ●**phenytoin**; metabolism of clozapine and quetiapine accelerated by ●**phenytoin** (reduced plasma concentration); plasma concentration of clozapine possibly increased or decreased by ●**valproate**; increased risk of side-effects including neutropenia when olanzapine given with ●**valproate**
- Antifungals: plasma concentration of aripiprazole possibly increased by ●**itraconazole** (reduce dose of aripiprazole—consult aripiprazole product literature);

Antipsychotics● Antifungals (*continued*)

side-effects of risperidone possibly increased by ●**itraconazole**; plasma concentration of haloperidol possibly increased by ●**itraconazole**; plasma concentration of quetiapine possibly increased by ●**imidazoles** and ●**triazoles**—manufacturer of quetiapine advises avoid concomitant use; increased risk of ventricular arrhythmias when pimozone given with ●**imidazoles** or ●**triazoles**—avoid concomitant use

- Antimalarials: avoidance of droperidol, haloperidol, phenothiazines and pimozone advised by manufacturer of ●**piperazine with arteminol** (possible risk of ventricular arrhythmias); avoidance of antipsychotics advised by manufacturer of ●**artemether with lumefantrine**; increased risk of ventricular arrhythmias when droperidol given with ●**chloroquine** and ●**hydroxychloroquine** or ●**quinine**—avoid concomitant use; manufacturer of amisulpride advises avoid concomitant use with ●**mefloquine**; possible increased risk of ventricular arrhythmias when haloperidol given with ●**mefloquine** or ●**quinine**—avoid concomitant use; increased risk of ventricular arrhythmias when pimozone given with ●**mefloquine** or ●**quinine**—avoid concomitant use
- Antimuscarinics: increased risk of antimuscarinic side-effects when clozapine given with ●**antimuscarinics**; plasma concentration of phenothiazines reduced by ●**antimuscarinics**, but risk of antimuscarinic side-effects increased; effects of haloperidol possibly reduced by ●**antimuscarinics**
- Antipsychotics: increased risk of ventricular arrhythmias when amisulpride, pimozone or sulpiride given with ●**droperidol**—avoid concomitant use; increased risk of ventricular arrhythmias when phenothiazines that prolong the QT interval given with ●**droperidol**—avoid concomitant use; avoid concomitant use of clozapine with depot formulation of ●**flupentixol**, ●**fluphenazine**, ●**haloperidol**, ●**pipotiazine**, ●**risperidone** or ●**zuclopenthixol** as cannot be withdrawn quickly if neutropenia occurs; increased risk of ventricular arrhythmias when sulpiride given with ●**haloperidol**; chlorpromazine possibly increases plasma concentration of ●**haloperidol**; increased risk of ventricular arrhythmias when droperidol given with ●**haloperidol**—avoid concomitant use; increased risk of ventricular arrhythmias when pimozone given with ●**phenothiazines**—avoid concomitant use; increased risk of ventricular arrhythmias when pimozone given with ●**sulpiride**
- Antivirals: plasma concentration of pimozone possibly increased by ●**atazanavir**—avoid concomitant use; plasma concentration of aripiprazole possibly increased by ●**atazanavir**, ●**darunavir**, ●**fosamprenavir**, ●**indinavir**, ●**lopinavir**, ●**ritonavir**, ●**saquinavir** and ●**tipranavir** (reduce dose of aripiprazole—consult aripiprazole product literature); plasma concentration of quetiapine possibly increased by ●**atazanavir**, ●**boceprevir**, ●**darunavir**, ●**fosamprenavir**, ●**indinavir**, ●**lopinavir**, ●**ritonavir**, ●**saquinavir**, ●**telaprevir** and ●**tipranavir**—manufacturer of quetiapine advises avoid concomitant use; avoidance of pimozone advised by manufacturer of ●**boceprevir** and ●**telaprevir**; plasma concentration of aripiprazole possibly reduced by ●**efavirenz** and ●**nevirapine** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); plasma concentration of pimozone possibly increased by ●**efavirenz**, ●**indinavir** and ●**saquinavir** (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of pimozone increased by ●**fosamprenavir** and ●**ritonavir** (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of olanzapine reduced by ●**ritonavir**—consider increasing dose of olanzapine; avoidance of cloz-

Antipsychotics

- **Antivirals (continued)**
apine advised by manufacturer of ● **ritonavir** (increased risk of toxicity); plasma concentration of antipsychotics possibly increased by ● **ritonavir**; increased risk of ventricular arrhythmias when clozapine, haloperidol or phenothiazines given with ● **saquinavir**—avoid concomitant use
- **Anxiolytics and Hypnotics**: increased sedative effect when antipsychotics given with ● **anxiolytics and hypnotics**; plasma concentration of haloperidol possibly increased by ● **alprazolam**; increased risk of hypotension, bradycardia and respiratory depression when intramuscular olanzapine given with *parenteral* ● **benzodiazepines**; serious adverse events reported with concomitant use of clozapine and ● **benzodiazepines** (causality not established); plasma concentration of haloperidol increased by ● **bupropion**
- **Aprepitant**: avoidance of pimozone advised by manufacturer of ● **aprepitant**
- **Atomoxetine**: increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with ● **atomoxetine**
- **Beta-blockers**: enhanced hypotensive effect when phenothiazines given with ● **beta-blockers**; plasma concentration of both drugs may increase when chlorpromazine given with ● **propranolol**; increased risk of ventricular arrhythmias when droperidol or zuclopenthixol given with ● **sotalol**—avoid concomitant use; possible increased risk of ventricular arrhythmias when haloperidol given with ● **sotalol**—avoid concomitant use; increased risk of ventricular arrhythmias when amisulpride, phenothiazines, pimozone or sulpiride given with ● **sotalol**
- Calcium-channel Blockers**: enhanced hypotensive effect when antipsychotics given with ● **calcium-channel blockers**
- Clonidine**: enhanced hypotensive effect when phenothiazines given with ● **clonidine**
- **Cobicistat**: plasma concentration of pimozone possibly increased by ● **cobicistat**—manufacturer of cobicistat advises avoid concomitant use
- **Cytotoxics**: avoid concomitant use of clozapine with ● **cytotoxics** (increased risk of agranulocytosis); possible increased risk of ventricular arrhythmias when haloperidol given with ● **bosutinib**; caution with pimozone advised by manufacturer of ● **erlotinib**; avoidance of pimozone advised by manufacturer of ● **lapatinib**; possible increased risk of ventricular arrhythmias when amisulpride, chlorpromazine, haloperidol, pimozone, sulpiride or zuclopenthixol given with ● **vandetanib**—avoid concomitant use; increased risk of ventricular arrhythmias when haloperidol given with ● **arsenic trioxide**; increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with ● **arsenic trioxide**
- Deferasirox**: avoidance of clozapine advised by manufacturer of ● **deferasirox**
- Desferrioxamine**: manufacturer of levomepromazine advises avoid concomitant use with ● **desferrioxamine**; avoidance of prochlorperazine advised by manufacturer of ● **desferrioxamine**
- Diazoxide**: enhanced hypotensive effect when phenothiazines given with ● **diazoxide**
- **Diuretics**: risk of ventricular arrhythmias with amisulpride increased by hypokalaemia caused by ● **diuretics**; risk of ventricular arrhythmias with pimozone increased by hypokalaemia caused by ● **diuretics** (avoid concomitant use); enhanced hypotensive effect when phenothiazines given with ● **diuretics**
- Dopaminergics**: increased risk of extrapyramidal side-effects when antipsychotics given with ● **amantadine**; antipsychotics antagonise effects of ● **apomorphine**, ● **levodopa** and ● **pergolide**; antipsychotics antagonise hypoprolactinaemic and antiparkinsonian effects of

Antipsychotics**Dopaminergics (continued)**

- **bromocriptine** and ● **cabergoline**; manufacturer of amisulpride advises avoid concomitant use of ● **levodopa** (antagonism of effect); avoidance of antipsychotics advised by manufacturer of ● **pramipexole**, ● **ropinirole** and ● **rotigotine** (antagonism of effect)
 - **Grapefruit Juice**: plasma concentration of quetiapine possibly increased by ● **grapefruit juice**—manufacturer of quetiapine advises avoid concomitant use
 - Histamine**: antipsychotics theoretically antagonise effects of ● **histamine**—manufacturer of histamine advises avoid concomitant use
 - **Hormone Antagonists**: manufacturer of droperidol advises avoid concomitant use with ● **tamoxifen** (risk of ventricular arrhythmias)
 - **Ivabradine**: increased risk of ventricular arrhythmias when pimozone given with ● **ivabradine**
 - **Lithium**: increased risk of extrapyramidal side-effects and possibly neurotoxicity when clozapine, flupentixol, haloperidol, phenothiazines, risperidone or zuclopenthixol given with ● **lithium**; possible risk of toxicity when olanzapine given with ● **lithium**; increased risk of extrapyramidal side-effects when sulpiride given with ● **lithium**
 - Memantine**: effects of antipsychotics possibly reduced by ● **memantine**
 - Methylodopa**: enhanced hypotensive effect when antipsychotics given with ● **methylodopa** (also increased risk of extrapyramidal effects)
 - Metoclopramide**: increased risk of extrapyramidal side-effects when antipsychotics given with ● **metoclopramide**
 - Moxonidine**: enhanced hypotensive effect when phenothiazines given with ● **moxonidine**
 - Muscle Relaxants**: promazine possibly enhances effects of ● **suxamethonium**
 - Nitrates**: enhanced hypotensive effect when phenothiazines given with ● **nitrates**
 - **Penicillamine**: avoid concomitant use of clozapine with ● **penicillamine** (increased risk of agranulocytosis)
 - **Pentamidine Isetionate**: increased risk of ventricular arrhythmias when amisulpride or droperidol given with ● **pentamidine isetionate**—avoid concomitant use; increased risk of ventricular arrhythmias when phenothiazines given with ● **pentamidine isetionate**
 - Sodium Benzoate**: haloperidol possibly reduces effects of ● **sodium benzoate**
 - Sodium Oxybate**: antipsychotics possibly enhance effects of ● **sodium oxybate**
 - Sodium Phenylbutyrate**: haloperidol possibly reduces effects of ● **sodium phenylbutyrate**
 - Sympathomimetics**: antipsychotics antagonise hypertensive effect of ● **sympathomimetics**; antipsychotic effects of chlorpromazine possibly antagonised by ● **dexamfetamine**; chlorpromazine possibly reduces effects of ● **lisdexamfetamine**; side-effects of risperidone possibly increased by ● **methylphenidate**
 - **Tacrolimus**: manufacturer of droperidol advises avoid concomitant use with ● **tacrolimus** (risk of ventricular arrhythmias)
 - Tetrabenazine**: increased risk of extrapyramidal side-effects when antipsychotics given with ● **tetrabenazine**
 - Ulcer-healing Drugs**: effects of antipsychotics, chlorpromazine and clozapine possibly enhanced by ● **cimetidine**; plasma concentration of clozapine possibly reduced by ● **omeprazole**; absorption of sulpiride reduced by ● **sucralfate**
 - Vasodilator Antihypertensives**: enhanced hypotensive effect when phenothiazines given with ● **hydralazine**, ● **minoxidil** or ● **sodium nitroprusside**
- Antivirals** see individual drugs

Anxiolytics and Hypnotics

ACE Inhibitors: enhanced hypotensive effect when anxiolytics and hypnotics given with **ACE inhibitors**

Adrenergic Neurone Blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with **adrenergic neurone blockers**

Alcohol: increased sedative effect when anxiolytics and hypnotics given with **alcohol**

Alpha-blockers: enhanced hypotensive and sedative effects when anxiolytics and hypnotics given with **alpha-blockers**

Anaesthetics, General: increased sedative effect when anxiolytics and hypnotics given with **general anaesthetics**

Analgesics: metabolism of midazolam possibly inhibited by **fentanyl**; increased sedative effect when anxiolytics and hypnotics given with **opioid analgesics**

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when anxiolytics and hypnotics given with **angiotensin-II receptor antagonists**

- Antibacterials: metabolism of midazolam inhibited by **clarithromycin**, **erythromycin** and **telithromycin** (increased plasma concentration with increased sedation); plasma concentration of buspirone increased by **erythromycin** (reduce dose of buspirone); metabolism of zopiclone inhibited by **erythromycin**; metabolism of benzodiazepines possibly accelerated by **rifampicin** (reduced plasma concentration); metabolism of diazepam and zaleplon accelerated by **rifampicin** (reduced plasma concentration); metabolism of buspirone possibly accelerated by **rifampicin**; metabolism of zolpidem accelerated by **rifampicin** (reduced plasma concentration and reduced effect); plasma concentration of zopiclone significantly reduced by **rifampicin**; metabolism of diazepam inhibited by **isoniazid**

Anticoagulants: chloral may transiently enhance anticoagulant effect of **coumarins**

- Antidepressants: plasma concentration of alprazolam increased by **fluoxetine**; plasma concentration of melatonin increased by **fluvoxamine**—avoid concomitant use; plasma concentration of some benzodiazepines increased by **fluvoxamine**; sedative effects possibly increased when zolpidem given with **sertraline**; manufacturer of buspirone advises avoid concomitant use with **MAOIs**; avoidance of buspirone for 14 days after stopping **tranylcypromine** advised by manufacturer of tranylcypromine; plasma concentration of *oral* midazolam possibly reduced by **St John's wort**; increased sedative effect when anxiolytics and hypnotics given with **mirtazapine**, **tricyclic-related antidepressants** or **tricyclics**

Antiepileptics: plasma concentration of clonazepam often reduced by **carbamazepine**, **phenobarbital** and **phenytoin**; plasma concentration of midazolam reduced by **carbamazepine** and **perampanel**; increased sedative effect when anxiolytics and hypnotics given with **phenobarbital**; diazepam increases or decreases plasma concentration of **phenytoin**; benzodiazepines possibly increase or decrease plasma concentration of **phenytoin**; plasma concentration of clobazam increased by **stiripentol**; increased risk of side-effects when clonazepam given with **valproate**; clobazam possibly increases plasma concentration of **valproate**; plasma concentration of diazepam and lorazepam possibly increased by **valproate**

- Antifungals: plasma concentration of diazepam and midazolam increased by **fluconazole** (risk of prolonged sedation); plasma concentration of alprazolam increased by **itraconazole**; plasma concentration of midazolam increased by **itraconazole**, **posaconazole** and **voriconazole** (risk of prolonged sedation); plasma concentration of buspirone

Anxiolytics and Hypnotics

- Antifungals (*continued*)

increased by **itraconazole** (reduce dose of buspirone); plasma concentration of diazepam increased by **voriconazole** (risk of prolonged sedation)

Antihistamines: increased sedative effect when anxiolytics and hypnotics given with **antihistamines**

- Antipsychotics: increased sedative effect when anxiolytics and hypnotics given with **antipsychotics**; alprazolam possibly increases plasma concentration of **haloperidol**; buspirone increases plasma concentration of **haloperidol**; serious adverse events reported with concomitant use of benzodiazepines and **clozapine** (causality not established); increased risk of hypotension, bradycardia and respiratory depression when *parenteral* benzodiazepines given with *intramuscular* **olanzapine**
- Antivirals: plasma concentration of midazolam possibly increased by **atazanavir**—avoid concomitant use of *oral* midazolam; plasma concentration of *oral* midazolam increased by **boceprevir**—manufacturer of boceprevir advises avoid concomitant use; increased risk of prolonged sedation when midazolam given with **efavirenz**—avoid concomitant use; plasma concentration of midazolam possibly increased by **fosamprenavir**, **indinavir**, **ritonavir** and **telaprevir** (risk of prolonged sedation)—avoid concomitant use of *oral* midazolam; increased risk of prolonged sedation when alprazolam given with **indinavir**—avoid concomitant use; plasma concentration of anxiolytics and hypnotics possibly increased by **ritonavir**; plasma concentration of alprazolam, diazepam, flurazepam and zolpidem possibly increased by **ritonavir** (risk of extreme sedation and respiratory depression—avoid concomitant use); plasma concentration of buspirone increased by **ritonavir** (increased risk of toxicity); plasma concentration of midazolam increased by **saquinavir** (risk of prolonged sedation)—avoid concomitant use of *oral* midazolam)
- Aprepitant: plasma concentration of midazolam increased by **aprepitant** (risk of prolonged sedation)
- Beta-blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with **calcium-channel blockers**; midazolam increases absorption of **lercanidipine**; plasma concentration of buspirone increased by **diltiazem** and **verapamil** (reduce dose of buspirone); metabolism of midazolam inhibited by **diltiazem** and **verapamil** (increased plasma concentration with increased sedation)
- Cardiac Glycosides: alprazolam increases plasma concentration of **digoxin** (increased risk of toxicity)
- Clonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with **clonidine**
- Cobicistat: avoidance of *oral* midazolam advised by manufacturer of **cobicistat**
- Cytotoxics: plasma concentration of midazolam increased by **crizotinib** and **nilotinib**
- Deferasirox: plasma concentration of midazolam possibly reduced by **deferasirox**
- Diazoxide: enhanced hypotensive effect when anxiolytics and hypnotics given with **diazoxide**
- Disulfiram: metabolism of benzodiazepines inhibited by **disulfiram** (increased sedative effects); increased risk of temazepam toxicity when given with **disulfiram**
- Diuretics: enhanced hypotensive effect when anxiolytics and hypnotics given with **diuretics**; administration of chloral with *parenteral* **furosemide** may displace thyroid hormone from binding sites
- Dopaminergics: benzodiazepines possibly antagonise effects of **levodopa**

Anxiolytics and Hypnotics (continued)

- Grapefruit Juice: plasma concentration of *oral* midazolam possibly increased by **grapefruit juice**; plasma concentration of buspirone increased by **grapefruit juice**
- Ivacaftor: plasma concentration of midazolam increased by **ivacaftor**
- Lipid-regulating Drugs: plasma concentration of midazolam possibly increased by **atorvastatin**
- Lithium: increased risk of neurotoxicity when clonazepam given with **lithium**
- Lofexidine: increased sedative effect when anxiolytics and hypnotics given with **lofexidine**
- Methylodopa: enhanced hypotensive effect when anxiolytics and hypnotics given with **methylodopa**
- Methylthioninium: possible risk of CNS toxicity when buspirone given with **methylthioninium**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)
- Moxonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with **moxonidine**; sedative effects possibly increased when benzodiazepines given with **moxonidine**
- Muscle Relaxants: increased sedative effect when anxiolytics and hypnotics given with **baclofen** or **tizanidine**
- Nitrates: enhanced hypotensive effect when anxiolytics and hypnotics given with **nitrates**
- Oestrogens: plasma concentration of melatonin increased by **oestrogens**; plasma concentration of chlorthalidopoxide, diazepam and nitrazepam possibly increased by **oestrogens**; plasma concentration of lorazepam, oxazepam and temazepam possibly reduced by **oestrogens**
- Probenecid: excretion of lorazepam reduced by **probenecid** (increased plasma concentration); excretion of nitrazepam possibly reduced by **probenecid** (increased plasma concentration)
- Progestogens: plasma concentration of chlorthalidopoxide, diazepam and nitrazepam possibly increased by **progestogens**; plasma concentration of lorazepam, oxazepam and temazepam possibly reduced by **progestogens**
- Sodium Oxybate: benzodiazepines enhance effects of **sodium oxybate** (avoid concomitant use)
- Theophylline: effects of benzodiazepines possibly reduced by **theophylline**
- Ulcer-healing Drugs: plasma concentration of melatonin increased by **cimetidine**; metabolism of benzodiazepines, clomethiazole and zaleplon inhibited by **cimetidine** (increased plasma concentration); metabolism of diazepam possibly inhibited by **esomeprazole** and **omeprazole** (increased plasma concentration)
- Vasodilator Antihypertensives: enhanced hypotensive effect when anxiolytics and hypnotics given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Apixaban

- Analgesics: increased risk of haemorrhage when anticoagulants given with **intravenous diclofenac** (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with **ketorolac** (avoid concomitant use, including low-dose heparins)
- Antibacterials: plasma concentration of apixaban reduced by **rifampicin**
- Anticoagulants: increased risk of haemorrhage when apixaban given with other **anticoagulants** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when other anticoagulants given with **dabigatran** and **rivaroxaban** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Apixaban (continued)

- Antifungals: manufacturer of apixaban advises avoid concomitant use with **itraconazole**, **posaconazole** and **voriconazole**
- Antivirals: manufacturer of apixaban advises avoid concomitant use with **atazanavir**, **boceprevir**, **darunavir**, **fosamprenavir**, **indinavir**, **lopinavir**, **ritonavir**, **saquinavir** and **tipranavir**
- Sulfinpyrazone: increased risk of bleeding when apixaban given with **sulfinpyrazone**

Apomorphine

- Antipsychotics: effects of apomorphine antagonised by **antipsychotics**
- Dopaminergics: effects of apomorphine possibly enhanced by **entacapone**
- 5HT₂-receptor Antagonists: possible increased hypotensive effect when apomorphine given with **ondansetron**—avoid concomitant use
- Memantine: effects of dopaminergics possibly enhanced by **memantine**
- Methylodopa: antiparkinsonian effect of dopaminergics antagonised by **methylodopa**

Apraclonidine

- Antidepressants: manufacturer of apraclonidine advises avoid concomitant use with **MAOIs, tricyclic-related antidepressants** and **tricyclics**
- Sympathomimetics: manufacturer of apraclonidine advises avoid concomitant use with **sympathomimetics**

Aprepitant

- Note** Fosaprepitant is a prodrug of aprepitant
- Antibacterials: plasma concentration of aprepitant possibly increased by **clarithromycin** and **tetracycline**; plasma concentration of aprepitant reduced by **rifampicin**
- Anticoagulants: aprepitant possibly reduces anticoagulant effect of **warfarin**
- Antidepressants: manufacturer of aprepitant advises avoid concomitant use with **St John's wort**
- Antidiabetics: aprepitant reduces plasma concentration of **tolbutamide**
- Antiepileptics: plasma concentration of aprepitant possibly reduced by **carbamazepine**, **phenobarbital** and **phenytoin**
- Antipsychotics: manufacturer of aprepitant advises avoid concomitant use with **pimozide**
- Antivirals: plasma concentration of aprepitant possibly increased by **ritonavir**
- Anxiolytics and Hypnotics: aprepitant increases plasma concentration of **midazolam** (risk of prolonged sedation)
- Calcium-channel Blockers: plasma concentration of both drugs may increase when aprepitant given with **diltiazem**
- Corticosteroids: aprepitant inhibits metabolism of **dexamethasone** and **methylprednisolone** (reduce dose of dexamethasone and methylprednisolone)
- Cytotoxics: aprepitant possibly increases the plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Dapoxetine: manufacturer of dapoxetine advises dose reduction when aprepitant given with **dapoxetine** (see Dose under Dapoxetine, BNF section 7.4.6)
- Lipid-regulating Drugs: manufacturer of lomitapide advises dose reduction when fosaprepitant given with **lomitapide** (see Dose under Lomitapide, BNF section 2.12)
- Oestrogens: aprepitant possibly causes contraceptive failure of hormonal contraceptives containing **oestrogens** (alternative contraception recommended)
 - Progestogens: aprepitant possibly causes contraceptive failure of hormonal contraceptives containing **progestogens** (alternative contraception recommended)

Aripiprazole *see* Antipsychotics**Arsenic Trioxide**

- Anti-arrhythmics: increased risk of ventricular arrhythmias when arsenic trioxide given with **•amiodarone** or **•disopyramide**
- Antibacterials: increased risk of ventricular arrhythmias when arsenic trioxide given with **•erythromycin**, **•levofloxacin** or **•moxifloxacin**
- Antidepressants: increased risk of ventricular arrhythmias when arsenic trioxide given with **•amitriptyline** or **•clomipramine**
- Antifungals: increased risk of ventricular arrhythmias when arsenic trioxide given with **•amphotericin**
- Antimalarials: avoidance of arsenic trioxide advised by manufacturer of **•piperazine with arteminol** (possible risk of ventricular arrhythmias)
- Antipsychotics: increased risk of ventricular arrhythmias when arsenic trioxide given with **•antipsychotics** that prolong the QT interval; increased risk of ventricular arrhythmias when arsenic trioxide given with **•haloperidol**; avoid concomitant use of cytotoxics with **•clozapine** (increased risk of agranulocytosis)
- Beta-blockers: increased risk of ventricular arrhythmias when arsenic trioxide given with **•sotalol**
- Cytotoxics: possible increased risk of ventricular arrhythmias when arsenic trioxide given with **•vandetanib**—avoid concomitant use
- Diuretics: risk of ventricular arrhythmias with arsenic trioxide increased by hypokalaemia caused by **•acetazolamide**, **•loop diuretics** or **•thiazides and related diuretics**
- Lithium: increased risk of ventricular arrhythmias when arsenic trioxide given with **•lithium**

Artemether with Lumefantrine

- Anti-arrhythmics: manufacturer of artemether with lumefantrine advises avoid concomitant use with **•amiodarone**, **•disopyramide** and **•flecainide** (risk of ventricular arrhythmias)
 - Antibacterials: manufacturer of artemether with lumefantrine advises avoid concomitant use with **•macrolides** and **•quinolones**
 - Antidepressants: avoidance of antimalarials advised by manufacturer of **•citalopram** and **•escitalopram** (risk of ventricular arrhythmias); manufacturer of artemether with lumefantrine advises avoid concomitant use with **•antidepressants**
 - Antifungals: manufacturer of artemether with lumefantrine advises avoid concomitant use with **•imidazoles** and **•triazoles**
 - Antimalarials: manufacturer of artemether with lumefantrine advises avoid concomitant use with **•antimalarials**; increased risk of ventricular arrhythmias when artemether with lumefantrine given with **•quinine**
 - Antipsychotics: manufacturer of artemether with lumefantrine advises avoid concomitant use with **•antipsychotics**
 - Antivirals: manufacturer of artemether with lumefantrine advises caution with **•atazanavir**, **•fosamprenavir**, **•indinavir**, **•lopinavir**, **•ritonavir**, **•saquinavir** and **•tipranavir**; avoidance of artemether with lumefantrine advised by manufacturer of **•boceprevir**; plasma concentration of lumefantrine increased by **•darunavir**; plasma concentration of artemether with lumefantrine reduced by **•etravirine**
 - Beta-blockers: manufacturer of artemether with lumefantrine advises avoid concomitant use with **•metoprolol** and **•sotalol**
 - Cytotoxics: possible increased risk of ventricular arrhythmias when artemether with lumefantrine given with **•vandetanib**—avoid concomitant use
- Grapefruit Juice: plasma concentration of artemether with lumefantrine possibly increased by **•grapefruit juice**

Artemether with Lumefantrine (*continued*)

- Histamine: avoidance of antimalarials advised by manufacturer of **•histamine**
- Ulcer-healing Drugs: manufacturer of artemether with lumefantrine advises avoid concomitant use with **•cimetidine**
- Vaccines: antimalarials inactivate **•oral typhoid vaccine**—see p. 626
- Ascorbic acid** *see* Vitamins
- Asenapine** *see* Antipsychotics
- Aspirin**
- Adsorbents: adsorption of aspirin possibly reduced by **•kaolin**
- Anaesthetics, General: aspirin possibly enhances effects of **•thiopental**
- Analgesics: avoid concomitant use of aspirin with **•NSAIDs** (increased side-effects); antiplatelet effect of aspirin possibly reduced by **•ibuprofen**
 - Antacids: excretion of aspirin increased by alkaline urine due to some **•antacids**
 - Anticoagulants: increased risk of bleeding when aspirin given with **•coumarins** or **•phenindione** (due to antiplatelet effect); aspirin enhances anti-coagulant effect of **•heparins**
 - Antidepressants: increased risk of bleeding when aspirin given with **•SSRIs** or **•venlafaxine**
 - Antiepileptics: aspirin enhances effects of **•phenytoin** and **•valproate**
 - Clopidogrel: increased risk of bleeding when aspirin given with **•clopidogrel**
 - Corticosteroids: increased risk of gastro-intestinal bleeding and ulceration when aspirin given with **•corticosteroids**, also corticosteroids reduce plasma concentration of salicylate
 - Cytotoxics: aspirin reduces excretion of **•methotrexate** (increased risk of toxicity); aspirin possibly reduces renal excretion of **•pemetrexed**—consult product literature
 - Diuretics: increased risk of toxicity when high-dose aspirin given with **•acetazolamide**; aspirin antagonises diuretic effect of **•spironolactone**; possible increased risk of toxicity when high-dose aspirin given with **•loop diuretics** (also possible reduced effect of loop diuretics)
- Iloprost: increased risk of bleeding when aspirin given with **•iloprost**
- Leukotriene Receptor Antagonists: aspirin increases plasma concentration of **•zafirlukast**
- Metoclopramide: rate of absorption of aspirin increased by **•metoclopramide** (enhanced effect)
- Probenecid: aspirin antagonises effects of **•probenecid**
- Sulfinpyrazone: aspirin antagonises effects of **•sulfinpyrazone**
- Atazanavir**
- Antacids: absorption of atazanavir reduced by **•antacids** (give at least 2 hours before or 1 hour after antacids)
- Anti-arrhythmics: atazanavir possibly increases plasma concentration of **•amiodarone** and **•lidocaine**
 - Antibacterials: plasma concentration of both drugs increased when atazanavir given with **•clarithromycin**; atazanavir increases plasma concentration of **•rifabutin** (reduce dose of rifabutin); plasma concentration of atazanavir reduced by **•rifampicin**—avoid concomitant use; avoidance of concomitant atazanavir in severe renal and hepatic impairment advised by manufacturer of **•telithromycin**
 - Anticoagulants: atazanavir may enhance or reduce anticoagulant effect of **•warfarin**; avoidance of atazanavir advised by manufacturer of **•apixaban** and **•rivaroxaban**
 - Antidepressants: plasma concentration of atazanavir reduced by **•St John's wort**—avoid concomitant use
 - Antifungals: plasma concentration of atazanavir increased by **•posaconazole**; atazanavir increases or

Atazanavir

- **Antifungals** (*continued*)
 - decreases the plasma concentration of **voriconazole** and plasma concentration of atazanavir also reduced
- **Antimalarials**: caution with atazanavir advised by manufacturer of **artemether with lumefantrine**; atazanavir possibly increases plasma concentration of **quinine** (increased risk of toxicity)
- **Antimuscarinics**: avoidance of atazanavir advised by manufacturer of **darifenacin**; manufacturer of fesoterodine advises dose reduction when atazanavir given with **fesoterodine**—consult fesoterodine product literature
- **Antipsychotics**: atazanavir possibly increases plasma concentration of **aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); atazanavir possibly increases plasma concentration of **pimozide**—avoid concomitant use; atazanavir possibly increases plasma concentration of **quetiapine**—manufacturer of quetiapine advises avoid concomitant use
- **Antivirals**: plasma concentration of atazanavir reduced by **boceprevir**; absorption of atazanavir reduced by **didanosine tablets** (give at least 2 hours before or 1 hour after didanosine tablets); manufacturer of atazanavir advises avoid concomitant use with **efavirenz** (plasma concentration of atazanavir reduced); atazanavir boosted with ritonavir increases plasma concentration of **elvitegravir** (reduce dose of elvitegravir); avoid concomitant use of atazanavir with **indinavir**; atazanavir increases plasma concentration of **maraviroc** (consider reducing dose of maraviroc); plasma concentration of atazanavir possibly reduced by **nevirapine**—avoid concomitant use; increased risk of ventricular arrhythmias when atazanavir given with **saquinavir**—avoid concomitant use; atazanavir possibly reduces plasma concentration of **telaprevir**, also plasma concentration of atazanavir possibly increased; plasma concentration of atazanavir reduced by **tenofovir**, also plasma concentration of tenofovir possibly increased; atazanavir increases plasma concentration of **tipranavir** (also plasma concentration of atazanavir reduced)
- **Anxiolytics and Hypnotics**: atazanavir possibly increases plasma concentration of **midazolam**—avoid concomitant use of *oral* midazolam
- **Calcium-channel Blockers**: atazanavir increases plasma concentration of **diltiazem** (reduce dose of diltiazem); atazanavir possibly increases plasma concentration of **verapamil**
- **Ciclosporin**: atazanavir possibly increases plasma concentration of **ciclosporin**
- **Colchicine**: atazanavir possibly increases risk of **colchicine** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- **Cytotoxics**: atazanavir possibly increases plasma concentration of **axitinib** (reduce dose of axitinib—consult axitinib product literature); atazanavir possibly increases the plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; atazanavir possibly increases plasma concentration of **crizotinib** and **everolimus**—manufacturer of crizotinib and everolimus advises avoid concomitant use; atazanavir possibly increases plasma concentration of **pazopanib** (reduce dose of pazopanib); avoidance of atazanavir advised by manufacturer of **cabazitaxel**; atazanavir possibly inhibits metabolism of **irinotecan** (increased risk of toxicity)
- **Dapoxetine**: avoidance of atazanavir advised by manufacturer of **dapoxetine** (increased risk of toxicity)
- **Ergot Alkaloids**: atazanavir possibly increases plasma concentration of **ergot alkaloids**—avoid concomitant use

Atazanavir (*continued*)

- **Lipid-regulating Drugs**: possible increased risk of myopathy when atazanavir given with **atorvastatin** or **pravastatin**; possible increased risk of myopathy when atazanavir given with **rosuvastatin**—manufacturer of rosuvastatin advises avoid concomitant use; increased risk of myopathy when atazanavir given with **simvastatin** (avoid concomitant use)
- **Oestrogens**: atazanavir increases plasma concentration of **ethinylestradiol**
- **Orlistat**: absorption of atazanavir possibly reduced by **orlistat**
- **Progestogens**: atazanavir increases plasma concentration of **norethisterone**
- **Ranolazine**: atazanavir possibly increases plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use
- **Sildenafil**: atazanavir possibly increases side-effects of **sildenafil**
- **Sirolimus**: atazanavir possibly increases plasma concentration of **sirolimus**
- **Tacrolimus**: atazanavir possibly increases plasma concentration of **tacrolimus**
- **Ticagrelor**: atazanavir possibly increases plasma concentration of **ticagrelor**—manufacturer of ticagrelor advises avoid concomitant use
- **Ulcer-healing Drugs**: manufacturer of atazanavir advises adjust doses of both drugs when atazanavir given with **cimetidine** and **nizatidine**—consult atazanavir product literature; plasma concentration of atazanavir reduced by **famotidine** and **ranitidine** (adjust doses of both drugs—consult atazanavir product literature); plasma concentration of atazanavir reduced by **proton pump inhibitors**—avoid or adjust dose of both drugs (consult product literature)

Atenolol *see* Beta-blockers**Atomoxetine**

- **Analgesics**: increased risk of ventricular arrhythmias when atomoxetine given with **methadone**; possible increased risk of convulsions when atomoxetine given with **tramadol**
- **Anti-arrhythmics**: increased risk of ventricular arrhythmias when atomoxetine given with **amiodarone** or **disopyramide**
- **Antibacterials**: increased risk of ventricular arrhythmias when atomoxetine given with *parenteral* **erythromycin**; increased risk of ventricular arrhythmias when atomoxetine given with **moxifloxacin**
- **Antidepressants**: metabolism of atomoxetine possibly inhibited by **fluoxetine** and **paroxetine**; possible increased risk of convulsions when atomoxetine given with **antidepressants**; atomoxetine should not be started until 2 weeks after stopping **MAOIs**, also MAOIs should not be started until at least 2 weeks after stopping atomoxetine; increased risk of ventricular arrhythmias when atomoxetine given with **tricyclics**
- **Antimalarials**: increased risk of ventricular arrhythmias when atomoxetine given with **mefloquine**
- **Antipsychotics**: increased risk of ventricular arrhythmias when atomoxetine given with **antipsychotics** that prolong the QT interval
- **Beta-blockers**: increased risk of ventricular arrhythmias when atomoxetine given with **sotalol**
- **Bupropion**: possible increased risk of convulsions when atomoxetine given with **bupropion**
- **Diuretics**: risk of ventricular arrhythmias with atomoxetine increased by hypokalaemia caused by **diuretics**
- **Sympathomimetics, Beta₂**: Increased risk of cardiovascular side-effects when atomoxetine given with *parenteral* **salbutamol**

Atorvastatin *see* Statins

Atovaquone

- Antibacterials: manufacturer of atovaquone advises avoid concomitant use with **rifabutin** (plasma concentration of both drugs reduced); plasma concentration of atovaquone reduced by **●rifampicin** (and concentration of rifampicin increased)—avoid concomitant use; plasma concentration of atovaquone reduced by **tetracycline**
- Antivirals: plasma concentration of atovaquone reduced by **●efavirenz**—avoid concomitant use; atovaquone possibly reduces plasma concentration of **indinavir**; plasma concentration of atovaquone possibly reduced by **ritonavir**—manufacturer of atovaquone advises avoid concomitant use; atovaquone increases plasma concentration of **zidovudine** (increased risk of toxicity)
- Cytotoxics: atovaquone possibly increases plasma concentration of **etoposide**
- Histamine: avoidance of atovaquone advised by manufacturer of **histamine**
- Metoclopramide: plasma concentration of atovaquone reduced by **metoclopramide**—avoid concomitant use

Atracurium *see* Muscle Relaxants

Atropine *see* Antimuscarinics

Axitinib

- Antibacterials: plasma concentration of axitinib possibly increased by **clarithromycin**, **erythromycin** and **telithromycin** (reduce dose of axitinib—consult axitinib product literature); plasma concentration of axitinib possibly decreased by **rifabutin** (increase dose of axitinib—consult axitinib product literature); plasma concentration of axitinib decreased by **rifampicin** (increase dose of axitinib—consult axitinib product literature)
- Antidepressants: plasma concentration of axitinib possibly reduced by **St John's wort**—consider increasing dose of axitinib
- Antiepileptics: plasma concentration of axitinib possibly decreased by **carbamazepine**, **phenobarbital** and **phenytoin** (increase dose of axitinib—consult axitinib product literature)
- Antifungals: plasma concentration of axitinib possibly increased by **itraconazole** (reduce dose of axitinib—consult axitinib product literature)
- Antipsychotics: avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)
- Antivirals: plasma concentration of axitinib possibly increased by **atazanavir**, **indinavir**, **ritonavir** and **saquinavir** (reduce dose of axitinib—consult axitinib product literature)
- Corticosteroids: plasma concentration of axitinib possibly decreased by **dexamethasone** (increase dose of axitinib—consult axitinib product literature)
- Grapefruit juice: plasma concentration of axitinib possibly increased by **grapefruit juice**

Azathioprine

- ACE Inhibitors: increased risk of anaemia or leucopenia when azathioprine given with **captopril** especially in renal impairment; increased risk of anaemia when azathioprine given with **enalapril** especially in renal impairment
- Allopurinol: enhanced effects and increased toxicity of azathioprine when given with **●allopurinol** (reduce dose of azathioprine to one quarter of usual dose)
- Aminosalicylates: possible increased risk of leucopenia when azathioprine given with **aminosalicylates**
- Antibacterials: increased risk of haematological toxicity when azathioprine given with **●sulfamethoxazole** (as co-trimoxazole); increased risk of haematological toxicity when azathioprine given with **●trimethoprim** (also with co-trimoxazole)
- Anticoagulants: azathioprine possibly reduces anti-coagulant effect of **●coumarins**

Azathioprine (continued)

- Antivirals: myelosuppressive effects of azathioprine possibly enhanced by **●ribavirin**
- Febuxostat: avoidance of azathioprine advised by manufacturer of **●febuxostat**

Azilsartan *see* Angiotensin-II Receptor Antagonists

Azithromycin *see* Macrolides

Aztreonam

- Anticoagulants: aztreonam possibly enhances anti-coagulant effect of **●coumarins**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Baclofen *see* Muscle Relaxants

Balsalazide *see* Aminosaliculates

Bambuterol *see* Sympathomimetics, Beta₂

Beclometasone *see* Corticosteroids

Belimumab

- Vaccines: avoid concomitant use of belimumab with live **●vaccines** (*see* p. 604)

Bendamustine

- Antipsychotics: avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)

Bendroflumethiazide *see* Diuretics

Benperidol *see* Antipsychotics

Benzodiazepines *see* Anxiolytics and Hypnotics

Benzthiazide *see* Diuretics

Benzyllpenicillin *see* Penicillins

Beta-blockers

- Note** Since systemic absorption may follow topical application of beta-blockers to the eye the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind
- ACE Inhibitors: enhanced hypotensive effect when beta-blockers given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when beta-blockers given with **adrenergic neurone blockers**
- Alcohol: enhanced hypotensive effect when beta-blockers given with **alcohol**
- Aldesleukin: enhanced hypotensive effect when beta-blockers given with **aldesleukin**
- Alpha-blockers: enhanced hypotensive effect when beta-blockers given with **●alpha-blockers**, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Anaesthetics, General: enhanced hypotensive effect when beta-blockers given with **general anaesthetics**
- Anaesthetics, Local: propranolol increases risk of **●bupivacaine** toxicity
- Analgesics: hypotensive effect of beta-blockers antagonised by **NSAIDs**; plasma concentration of esmolol possibly increased by **morphine**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when beta-blockers given with **angiotensin-II receptor antagonists**
- Anti-arrhythmics: increased myocardial depression when beta-blockers given with **●anti-arrhythmics**; increased risk of ventricular arrhythmias when sotalol given with **●amiodarone**, **●disopyramide** or **●dronedrone**—avoid concomitant use; increased risk of bradycardia, AV block and myocardial depression when beta-blockers given with **●amiodarone**; plasma concentration of metoprolol and propranolol possibly increased by **dronedrone**; increased risk of myocardial depression and bradycardia when beta-blockers given with **●flecainide**; propranolol increases risk of **●lidocaine** toxicity; nadolol possibly increases risk of **lidocaine** toxicity; plasma concentration of metoprolol and propranolol increased by **propafenone**
- Antibacterials: increased risk of ventricular arrhythmias when sotalol given with **●moxifloxacin**—avoid concomitant use; metabolism of bisoprolol and propranolol accelerated by **●rifampicin** (plasma concentration significantly reduced); plasma concentra-

Beta-blockers

- Antibericals (*continued*)
tion of carvedilol, celiprolol and metoprolol reduced by **rifampicin**
- Antidepressants: plasma concentration of metoprolol increased by **citalopram** and **escitalopram**; increased risk of ventricular arrhythmias when sotalol given with **citalopram**—avoid concomitant use; avoidance of sotalol advised by manufacturer of **escitalopram** (risk of ventricular arrhythmias); plasma concentration of propranolol increased by **fluvoxamine**; plasma concentration of metoprolol possibly increased by **paroxetine**—increased risk of AV block (manufacturer of paroxetine advises avoid concomitant use in cardiac insufficiency); labetalol and propranolol increase plasma concentration of **imipramine**; enhanced hypotensive effect when beta-blockers given with **MAOIs**; increased risk of ventricular arrhythmias when sotalol given with **tricyclics**
- Antidiabetics: beta-blockers may mask warning signs of hypoglycaemia (such as tremor) with **anti-diabetics**; beta-blockers enhance hypoglycaemic effect of **insulin**
- Antiepileptics: plasma concentration of propranolol possibly reduced by **phenobarbital**
- Antihistamines: increased risk of ventricular arrhythmias when sotalol given with **mizolastine**—avoid concomitant use
- Antimalarials: avoidance of sotalol advised by manufacturer of **piperquine with artemimol** (possible risk of ventricular arrhythmias); avoidance of metoprolol and sotalol advised by manufacturer of **artemether with lumefantrine**; increased risk of bradycardia when beta-blockers given with **mefloquine**
- Antimuscarinics: increased risk of ventricular arrhythmias when sotalol given with **tolterodine**
- Antipsychotics: increased risk of ventricular arrhythmias when sotalol given with **droperidol** or **zuclopenthixol**—avoid concomitant use; possible increased risk of ventricular arrhythmias when sotalol given with **haloperidol**—avoid concomitant use; plasma concentration of both drugs may increase when propranolol given with **chlorpromazine**; increased risk of ventricular arrhythmias when sotalol given with **amisulpride**, **phenothiazines**, **pimozide** or **sulpride**; enhanced hypotensive effect when beta-blockers given with **phenothiazines**
- Antivirals: increased risk of ventricular arrhythmias when sotalol given with **saquinavir**—avoid concomitant use; avoidance of sotalol advised by manufacturer of **telaprevir** (risk of ventricular arrhythmias); avoidance of metoprolol for heart failure advised by manufacturer of **tipranavir**
- Anxiolytics and Hypnotics: enhanced hypotensive effect when beta-blockers given with **anxiolytics and hypnotics**
- Atomoxetine: increased risk of ventricular arrhythmias when sotalol given with **atomoxetine**
- Calcium-channel Blockers: enhanced hypotensive effect when beta-blockers given with **calcium-channel blockers**; possible severe hypotension and heart failure when beta-blockers given with **nifedipine**; increased risk of AV block and bradycardia when beta-blockers given with **diltiazem**; asystole, severe hypotension and heart failure when beta-blockers given with **verapamil** (see p. 107)
- Cardiac Glycosides: increased risk of AV block and bradycardia when beta-blockers given with **cardiac glycosides**
- Ciclosporin: carvedilol increases plasma concentration of **ciclosporin**
- Clonidine: increased risk of withdrawal hypertension when beta-blockers given with **clonidine** (withdraw

Beta-blockers

- Clonidine (*continued*)
beta-blockers several days before slowly withdrawing clonidine)
- Corticosteroids: hypotensive effect of beta-blockers antagonised by **corticosteroids**
- Cytotoxics: possible increased risk of ventricular arrhythmias when sotalol given with **bosutinib**; possible increased risk of bradycardia when beta-blockers given with **crizotinib**; possible increased risk of ventricular arrhythmias when sotalol given with **vandetanib**—avoid concomitant use; increased risk of ventricular arrhythmias when sotalol given with **arsenic trioxide**
- Diazoxide: enhanced hypotensive effect when beta-blockers given with **diazoxide**
- Diuretics: enhanced hypotensive effect when beta-blockers given with **diuretics**; risk of ventricular arrhythmias with sotalol increased by hypokalaemia caused by **loop diuretics** or **thiazides and related diuretics**
- Dopaminergics: enhanced hypotensive effect when beta-blockers given with **levodopa**
- Ergot Alkaloids: increased peripheral vasoconstriction when beta-blockers given with **ergotamine**
- Fingolimod: possible increased risk of bradycardia when beta-blockers given with **fingolimod**
- Hormone Antagonists: possible increased risk of bradycardia when carteolol, metoprolol, propranolol or sotalol given with **pasireotide**
- 5HT₁-receptor Agonists: propranolol increases plasma concentration of **rizatriptan** (manufacturer of rizatriptan advises halve dose and avoid within 2 hours of propranolol)
- Ivabradine: increased risk of ventricular arrhythmias when sotalol given with **ivabradine**
- Methyldopa: enhanced hypotensive effect when beta-blockers given with **methyldopa**
- Mirabegron: plasma concentration of metoprolol increased by **mirabegron**
- Moxislyle: possible severe postural hypotension when beta-blockers given with **moxislyle**
- Moxonidine: enhanced hypotensive effect when beta-blockers given with **moxonidine**
- Muscle Relaxants: propranolol enhances effects of **muscle relaxants**; enhanced hypotensive effect when beta-blockers given with **baclofen**; possible enhanced hypotensive effect and bradycardia when beta-blockers given with **tizanidine**
- Nitrates: enhanced hypotensive effect when beta-blockers given with **nitrates**
- Oestrogens: hypotensive effect of beta-blockers antagonised by **oestrogens**
- Parasympathomimetics: propranolol antagonises effects of **neostigmine** and **pyridostigmine**; increased risk of arrhythmias when beta-blockers given with **pilocarpine**
- Prostaglandins: enhanced hypotensive effect when beta-blockers given with **alprostadil**
- Ranolazine: avoidance of sotalol advised by manufacturer of **ranolazine**
- Sympathomimetics: increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers given with **adrenaline (epinephrine)**, also response to adrenaline (epinephrine) may be reduced; increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers given with **dobutamine**; possible increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers given with **noradrenaline (norepinephrine)**
- Thyroid Hormones: metabolism of propranolol accelerated by **levothyroxine**
- Ulcer-healing Drugs: plasma concentration of labetalol, metoprolol and propranolol increased by **cimetidine**

Beta-blockers (*continued*)

Vasodilator Antihypertensives: enhanced hypotensive effect when beta-blockers given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Bethahistine

Antihistamines: effect of bethahistine theoretically antagonised by **antihistamines**

Betamethasone *see* Corticosteroids**Betaxolol** *see* Beta-blockers**Bethanechol** *see* Parasympathomimetics**Bevacizumab**

- Antipsychotics: avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)

Bexarotene

- Antipsychotics: avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)
- Lipid-regulating Drugs: plasma concentration of bexarotene increased by **●gemfibrozil**—avoid concomitant use

Bezafibrate *see* Fibrates**Bicalutamide**

Anticoagulants: bicalutamide possibly enhances anticoagulant effect of **coumarins**

Biguanides *see* Antidiabetics**Bilastine** *see* Antihistamines**Bile Acid Sequestrants** *see* Colessevelam, Colestipol, and Colestyramine**Bile Acids**

Antacids: absorption of bile acids possibly reduced by **antacids**

- Ciclosporin: ursodeoxycholic acid increases absorption of **●ciclosporin**

Lipid-regulating Drugs: absorption of bile acids possibly reduced by **colestipol** and **colestyramine**

Bisoprolol *see* Beta-blockers**Bisphosphonates**

Antacids: absorption of bisphosphonates reduced by **antacids**

Antibacterials: increased risk of hypocalcaemia when bisphosphonates given with **aminoglycosides**

Calcium Salts: absorption of bisphosphonates reduced by **calcium salts**

- Cytotoxics: sodium clodronate increases plasma concentration of **●estramustine**

Iron: absorption of bisphosphonates reduced by **oral iron**

Bleomycin

- Antipsychotics: avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)

Cardiac Glycosides: bleomycin possibly reduces absorption of **digoxin tablets**

- Cytotoxics: increased pulmonary toxicity when bleomycin given with **●cisplatin**; increased risk of pulmonary toxicity when bleomycin given with **●brentuximab vedotin**—avoid concomitant use

Boceprevir

Analgesics: possible increased risk of prolonged sedation and respiratory depression when boceprevir given with **buprenorphine**; boceprevir possibly affects plasma concentration of **methadone**

- Antibacterials: manufacturer of boceprevir advises avoid concomitant use with **●rifampicin** (plasma concentration of boceprevir possibly reduced)

Anticoagulants: avoidance of boceprevir advised by manufacturer of **apixaban**

- Antiepileptics: manufacturer of boceprevir advises avoid concomitant use with **●carbamazepine**, **●phenobarbital** and **●phenytoin** (plasma concentration of boceprevir possibly reduced)
- Antimalarials: manufacturer of boceprevir advises avoid concomitant use with **●artemether with lumefantrine**
- Antipsychotics: manufacturer of boceprevir advises avoid concomitant use with **●pimozide**; boceprevir possibly increases plasma concentration of **●quetia-**

Boceprevir

- Antipsychotics (*continued*)

pine—manufacturer of quetiapine advises avoid concomitant use

- Antivirals: boceprevir reduces plasma concentration of **●atazanavir**; avoid concomitant use of boceprevir with **●darunavir**; effects of both drugs possibly reduced when boceprevir given with **●etravirine**; avoidance of boceprevir advised by manufacturer of **●fosamprenavir** and **●nevirapine**; manufacturers advise avoid concomitant use of boceprevir with **●lopinavir**; boceprevir increases plasma concentration of **●maraviroc** (consider reducing dose of maraviroc); plasma concentration of both drugs reduced when boceprevir given with **●ritonavir**
- Anxiolytics and Hypnotics: boceprevir increases plasma concentration of **oral ●midazolam**—manufacturer of boceprevir advises avoid concomitant use

Cardiac Glycosides: boceprevir possibly increases side-effects of **digoxin**

- Ciclosporin: boceprevir increases plasma concentration of **●ciclosporin**

- Cilostazol: boceprevir possibly increases plasma concentration of **●cilostazol** (see Dose under Cilostazol, BNF section 2.6.4)

Cobicistat: avoidance of boceprevir advised by manufacturer of **cobicistat**

- Cytotoxics: boceprevir possibly increases the plasma concentration of **●bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; manufacturer of boceprevir advises avoid concomitant use with **●dasatinib**, **●erlotinib**, **●gefitinib**, **●imatinib**, **●lapatinib**, **●nilotinib**, **●pazopanib**, **●sorafenib** and **●sunitinib**; manufacturer of ruxolitinib advises dose reduction when boceprevir given with **●ruxolitinib**—consult ruxolitinib product literature

- Ergot Alkaloids: manufacturer of boceprevir advises avoid concomitant use with **●ergot alkaloids**

- Lipid-regulating Drugs: boceprevir increases plasma concentration of **●atorvastatin** (reduce dose of atorvastatin); boceprevir increases plasma concentration of **●pravastatin**; manufacturers advise avoid concomitant use of boceprevir with **●simvastatin**

Progestogens: boceprevir increases plasma concentration of **●drospirenone** (increased risk of toxicity)

- Sirolimus: boceprevir increases plasma concentration of **●sirolimus** (increased risk of toxicity—reduce sirolimus dose)

- Tacrolimus: boceprevir increases plasma concentration of **●tacrolimus** (reduce dose of tacrolimus)

Bortezomib

Antipsychotics: avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)

Bosentan

Antibacterials: plasma concentration of bosentan reduced by **●rifampicin**—avoid concomitant use

Anticoagulants: manufacturer of bosentan recommends monitoring anticoagulant effect of **coumarins**

- Antidiabetics: increased risk of hepatotoxicity when bosentan given with **●glibenclamide**—avoid concomitant use

- Antifungals: plasma concentration of bosentan possibly increased by **●fluconazole**—avoid concomitant use; plasma concentration of bosentan possibly increased by **●itraconazole**

- Antivirals: avoidance of bosentan advised by manufacturer of **●elvitegravir** and **●tipranavir**; bosentan possibly reduces plasma concentration of **●indinavir**; plasma concentration of bosentan increased by **●lopinavir** and **●ritonavir** (consider reducing dose of bosentan); bosentan possibly reduces plasma concentration of **●telaprevir**, also plasma concentration of bosentan possibly increased

Bosentan (*continued*)

- Cyclosporin: plasma concentration of bosentan increased by ●**cyclosporin** (also plasma concentration of cyclosporin reduced—avoid concomitant use)
- Cobicistat: avoidance of bosentan advised by manufacturer of ●**cobicistat**
- Cytotoxics: bosentan possibly reduces plasma concentration of ●**bosutinib**—manufacturer of bosutinib advises avoid concomitant use
- Lipid-regulating Drugs: bosentan reduces plasma concentration of ●**simvastatin**
- Oestrogens: bosentan possibly causes contraceptive failure of hormonal contraceptives containing ●**oestrogens** (alternative contraception recommended)
- Progestogens: bosentan possibly causes contraceptive failure of hormonal contraceptives containing ●**progestogens** (alternative contraception recommended)
- Sildenafil: bosentan reduces plasma concentration of ●**sildenafil**, also plasma concentration of bosentan increased
- Tadalafil: bosentan reduces plasma concentration of ●**tadalafil**

Bosutinib

- Analgesics: possible increased risk of ventricular arrhythmias when bosutinib given with ●**methadone**
- Antacids: manufacturer of bosutinib advises separating administration with ●**antacids** by about 12 hours
- Anti-arrhythmics: possible increased risk of ventricular arrhythmias when bosutinib given with ●**amiodarone** and ●**disopyramide**; plasma concentration of bosutinib possibly increased by ●**dronedaron**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Antibacterials: plasma concentration of bosutinib possibly increased by ●**ciprofloxacin**, ●**clarithromycin**, ●**erythromycin** and ●**telithromycin**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; possible increased risk of ventricular arrhythmias when bosutinib given with ●**moxifloxacin**; plasma concentration of bosutinib possibly reduced by ●**rifabutin**—manufacturer of bosutinib advises avoid concomitant use; plasma concentration of bosutinib reduced by ●**rifampicin**—manufacturer of bosutinib advises avoid concomitant use
- Antidepressants: plasma concentration of bosutinib possibly reduced by ●**St John's wort**—manufacturer of bosutinib advises avoid concomitant use
- Antiepileptics: plasma concentration of bosutinib possibly reduced by ●**carbamazepine**, ●**phenobarbital** and ●**phenytoin**—manufacturer of bosutinib advises avoid concomitant use
- Antifungals: plasma concentration of bosutinib possibly increased by ●**fluconazole**, ●**itraconazole**, ●**posaconazole** and ●**voriconazole**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Antimalarials: possible increased risk of ventricular arrhythmias when bosutinib given with ●**chloroquine** and ●**hydroxychloroquine**
- Antipsychotics: possible increased risk of ventricular arrhythmias when bosutinib given with ●**haloperidol**; avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)
- Antivirals: plasma concentration of bosutinib possibly increased by ●**atazanavir**, ●**boceprevir**, ●**darunavir**, ●**fosamprenavir**, ●**indinavir**, ●**ritonavir**, ●**saquinavir** and ●**telaprevir**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; plasma concentration of bosutinib possibly reduced by ●**efavirenz** and ●**etravirine**—manufacturer of bosutinib advises avoid concomitant use
- Aprepitant: plasma concentration of bosutinib possibly increased by ●**aprepitant**—manufacturer of bosu-

Bosutinib

- Aprepitant (*continued*)
nib advises avoid or consider reducing dose of bosutinib
- Beta-blockers: possible increased risk of ventricular arrhythmias when bosutinib given with ●**sotalol**
- Bosentan: plasma concentration of bosutinib possibly reduced by ●**bosentan**—manufacturer of bosutinib advises avoid concomitant use
- Calcium-channel Blockers: plasma concentration of bosutinib possibly increased by ●**diltiazem** and ●**verapamil**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Cytotoxics: plasma concentration of bosutinib possibly increased by ●**imatinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Domperidone: manufacturer of bosutinib advises avoid concomitant use with ●**domperidone** (risk of ventricular arrhythmias)
- Grapefruit Juice: plasma concentration of bosutinib possibly increased by ●**grapefruit juice**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Modafinil: plasma concentration of bosutinib possibly reduced by ●**modafinil**—manufacturer of bosutinib advises avoid concomitant use
- Ulcer-healing Drugs: plasma concentration of bosutinib reduced by ●**lansoprazole**

Brentuximab vedotin

- Antibacterials: effects of brentuximab vedotin possibly reduced by ●**rifampicin**
- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)
- Cytotoxics: increased risk of pulmonary toxicity when brentuximab vedotin given with ●**bleomycin**—avoid concomitant use

Brimonidine

Antidepressants: manufacturer of brimonidine advises avoid concomitant use with ●**MAOIs**, ●**tricyclic-related antidepressants** and ●**tricyclics**

Brinzolamide *see* Diuretics**Bromocriptine**

- Alcohol: tolerance of bromocriptine reduced by ●**alcohol**
- Antibacterials: plasma concentration of bromocriptine increased by ●**erythromycin** (increased risk of toxicity); plasma concentration of bromocriptine possibly increased by ●**macrolides** (increased risk of toxicity)
- Antipsychotics: hypoprolactinaemic and antiparkinsonian effects of bromocriptine antagonised by ●**antipsychotics**
- Domperidone: hypoprolactinaemic effect of bromocriptine possibly antagonised by ●**domperidone**
- Hormone Antagonists: plasma concentration of bromocriptine increased by ●**octreotide**
- Memantine: effects of dopaminergics possibly enhanced by ●**memantine**
- Methylodopa: antiparkinsonian effect of dopaminergics antagonised by ●**methylodopa**
- Metoclopramide: hypoprolactinaemic effect of bromocriptine antagonised by ●**metoclopramide**
- Sympathomimetics: risk of toxicity when bromocriptine given with ●**isometheptene**

Bucilazine *see* Antihistamines**Budesonide** *see* Corticosteroids**Bumetanide** *see* Diuretics**Bupivacaine**

- Anti-arrhythmics: increased myocardial depression when bupivacaine given with ●**anti-arrhythmics**
- Beta-blockers: increased risk of bupivacaine toxicity when given with ●**propranolol**

Buprenorphine *see* Opioid Analgesics

Bupropion

- Antidepressants: bupropion possibly increases plasma concentration of **citalopram**; manufacturer of bupropion advises avoid for 2 weeks after stopping
 - **MAOIs**; manufacturer of bupropion advises avoid concomitant use with **moclobemide**; bupropion possibly increases plasma concentration of **tricyclics** (possible increased risk of convulsions)
- Antiepileptics: plasma concentration of bupropion reduced by **carbamazepine** and **phenytoin**; metabolism of bupropion inhibited by **valproate**
- Antivirals: metabolism of bupropion accelerated by **efavirenz** (reduced plasma concentration); plasma concentration of bupropion reduced by **ritonavir**
- Atomoxetine: possible increased risk of convulsions when bupropion given with **atomoxetine**
- Dopaminergics: increased risk of side-effects when bupropion given with **amantadine** or **levodopa**
- Hormone Antagonists: bupropion possibly inhibits metabolism of **tamoxifen** to active metabolite (avoid concomitant use)
- Methylthioninium: possible risk of CNS toxicity when bupropion given with **methylthioninium**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

Bupirone *see* Anxiolytics and Hypnotics

Busulfan

- Analgesics: metabolism of *intravenous* busulfan possibly inhibited by **paracetamol** (manufacturer of *intravenous* busulfan advises caution within 72 hours of paracetamol)
- Antibacterials: plasma concentration of busulfan increased by **metronidazole** (increased risk of toxicity)
 - Antiepileptics: plasma concentration of busulfan possibly reduced by **phenytoin**
 - Antifungals: metabolism of busulfan inhibited by **itraconazole** (increased risk of toxicity)
 - Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
 - Cytotoxics: increased risk of hepatotoxicity when busulfan given with **tioguanine**

Butyrophenones *see* Antipsychotics

Cabazitaxel

- Antibacterials: plasma concentration of cabazitaxel possibly increased by **clarithromycin** and **telithromycin**—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel; manufacturer of cabazitaxel advises avoid concomitant use with **rifabutin**; plasma concentration of cabazitaxel reduced by **rifampicin**—manufacturer of cabazitaxel advises avoid concomitant use
- Antidepressants: manufacturer of cabazitaxel advises avoid concomitant use with **St John's wort**
- Antiepileptics: manufacturer of cabazitaxel advises avoid concomitant use with **carbamazepine**, **phenobarbital** and **phenytoin**
- Antifungals: plasma concentration of cabazitaxel possibly increased by **itraconazole** and **voriconazole**—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Antivirals: manufacturer of cabazitaxel advises avoid concomitant use with **atazanavir**; plasma concentration of cabazitaxel possibly increased by **indinavir**, **ritonavir** and **sacquinavir**—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel

Cabergoline

- Antibacterials: plasma concentration of cabergoline increased by **erythromycin** (increased risk of toxicity); plasma concentration of cabergoline possibly increased by **macrolides** (increased risk of toxicity)

Cabergoline (*continued*)

- Antipsychotics: hypoprolactinaemic and anti-parkinsonian effects of cabergoline antagonised by **antipsychotics**
- Dopramidone: hypoprolactinaemic effect of cabergoline possibly antagonised by **dopramidone**
- Memantine: effects of dopaminergics possibly enhanced by **memantine**
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by **methyldopa**
- Metoclopramide: hypoprolactinaemic effect of cabergoline antagonised by **metoclopramide**

Caffeine citrate

- Anti-arrhythmics: caffeine citrate antagonises anti-arrhythmic effect of **adenosine**—manufacturer of adenosine advises avoid caffeine citrate for at least 12 hours before adenosine
- Antiepileptics: caffeine citrate possibly antagonises effects of **phenobarbital**; plasma concentration of caffeine citrate reduced by **phenytoin**
- Theophylline: manufacturer of caffeine citrate advises avoid concomitant use with **theophylline**
- Ulcer-healing Drugs: plasma concentration of caffeine citrate increased by **cimetidine**

Calcitriol *see* Vitamins

Calcium Salts

Note *see also* Antacids

- Antibacterials: calcium salts reduce absorption of **ciprofloxacin** and **tetracycline**
- Antivirals: calcium salts possibly reduce absorption of **dolutegravir**—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after calcium salts; manufacturer of rilpivirine advises give calcium salts 2 hours before or 4 hours after **rilpivirine**
- Bisphosphonates: calcium salts reduce absorption of **bisphosphonates**
- Cardiac Glycosides: large *intravenous* doses of calcium salts can precipitate arrhythmias when given with **cardiac glycosides**
- Corticosteroids: absorption of calcium salts reduced by **corticosteroids**
- Cytotoxics: calcium salts reduce absorption of **estradiol** (manufacturer of estradiol advises avoid concomitant administration)
- Diuretics: increased risk of hypercalcaemia when calcium salts given with **thiazides and related diuretics**
- Eltrombopag: calcium salts possibly reduce absorption of **eltrombopag** (give at least 4 hours apart)
- Fluorides: calcium salts reduce absorption of **fluorides**
- Iron: calcium salts reduce absorption of **oral iron**
- Thyroid Hormones: calcium salts reduce absorption of **levothyroxine**

Zinc: calcium salts reduce absorption of **zinc**

Calcium-channel Blockers

- Note** Dihydropyridine calcium-channel blockers include amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nimodipine
- ACE Inhibitors: enhanced hypotensive effect when calcium-channel blockers given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when calcium-channel blockers given with **adrenergic neurone blockers**
- Alcohol: enhanced hypotensive effect when calcium-channel blockers given with **alcohol**; verapamil possibly increases plasma concentration of **alcohol**
- Aldesleukin: enhanced hypotensive effect when calcium-channel blockers given with **aldesleukin**
- Aliskiren: verapamil increases plasma concentration of **aliskiren**
- Alpha-blockers: verapamil increases plasma concentration of **tamsulosin**; enhanced hypotensive effect when calcium-channel blockers given with **alpha-blockers**, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin

Calcium-channel Blockers (*continued*)

- Anaesthetics, General: enhanced hypotensive effect when calcium-channel blockers given with **general anaesthetics** or **isoflurane**; hypotensive effect of verapamil enhanced by **general anaesthetics** (also AV delay)
- Analgesics: hypotensive effect of calcium-channel blockers antagonised by **NSAIDs**; diltiazem inhibits metabolism of **alfentanil** (risk of prolonged or delayed respiratory depression)
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when calcium-channel blockers given with **angiotensin-II receptor antagonists**
- Anti-arrhythmics: increased risk of bradycardia, AV block and myocardial depression when diltiazem or verapamil given with **amiodarone**; increased risk of myocardial depression and asystole when verapamil given with **disopyramide** or **flecainide**; increased risk of bradycardia and myocardial depression when diltiazem and verapamil given with **dronedarone**; nifedipine increases plasma concentration of **dronedarone**
- Antibacterials: metabolism of calcium-channel blockers possibly inhibited by **clarithromycin**, **erythromycin** and **telithromycin** (increased risk of side-effects); manufacturer of lercanidipine advises avoid concomitant use with **erythromycin**; metabolism of diltiazem, nifedipine, nimodipine and verapamil accelerated by **rifampicin** (plasma concentration significantly reduced); plasma concentration of felodipine possibly reduced by **rifampicin**; metabolism of nicardipine possibly accelerated by **rifampicin** (possibly significantly reduced plasma concentration)
- Anticoagulants: verapamil possibly increases plasma concentration of **dabigatran** (see Dose under Dabigatran, BNf section 2.8.2)
- Antidepressants: metabolism of nifedipine possibly inhibited by **fluoxetine** (increased plasma concentration); diltiazem and verapamil increase plasma concentration of **imipramine**; enhanced hypotensive effect when calcium-channel blockers given with **MAOIs**; plasma concentration of amlodipine and felodipine possibly reduced by **St John's wort**; plasma concentration of verapamil significantly reduced by **St John's wort**; plasma concentration of nifedipine reduced by **St John's wort**; diltiazem and verapamil possibly increase plasma concentration of **tricyclics**
- Antidiabetics: glucose tolerance occasionally impaired when nifedipine given with **insulin**
- Antiepileptics: effects of felodipine reduced by **carbamazepine** and **phenytoin**; effects of dihydropyridines, nicardipine and nifedipine probably reduced by **carbamazepine**; diltiazem and verapamil enhance effects of **carbamazepine**; manufacturer of nimodipine advises avoid concomitant use with **carbamazepine** and **phenytoin** (plasma concentration of nimodipine possibly reduced); effects of calcium-channel blockers probably reduced by **phenobarbital**; manufacturer of nimodipine advises avoid concomitant use with **phenobarbital** (plasma concentration of nimodipine reduced); effects of verapamil reduced by **phenytoin**; diltiazem increases plasma concentration of **phenytoin** but also effect of diltiazem reduced
- Antifungals: negative inotropic effect possibly increased when calcium-channel blockers given with **itraconazole**; metabolism of dihydropyridines possibly inhibited by **itraconazole** (increased plasma concentration); metabolism of felodipine inhibited by **itraconazole** (increased plasma concentration); manufacturer of lercanidipine advises avoid concomitant use with **itraconazole**; plasma concentration of nifedipine increased by **micafungin**

Calcium-channel Blockers (*continued*)

- Antimalarials: possible increased risk of bradycardia when calcium-channel blockers given with **mefloquine**
- Antimuscarinics: avoidance of verapamil advised by manufacturer of **darifenacin**; verapamil increases plasma concentration of **solifenacin**
- Antipsychotics: enhanced hypotensive effect when calcium-channel blockers given with **antipsychotics**
- Antivirals: plasma concentration of diltiazem increased by **atazanavir** (reduce dose of diltiazem); plasma concentration of verapamil possibly increased by **atazanavir**; plasma concentration of diltiazem reduced by **efavirenz**; plasma concentration of calcium-channel blockers possibly increased by **ritonavir**; manufacturer of lercanidipine advises avoid concomitant use with **ritonavir**; caution with diltiazem, felodipine, nicardipine, nifedipine and verapamil advised by manufacturer of **telaprevir**; plasma concentration of amlodipine increased by **telaprevir** (consider reducing dose of amlodipine)
- Anxiolytics and Hypnotics: enhanced hypotensive effect when calcium-channel blockers given with **anxiolytics and hypnotics**; diltiazem and verapamil inhibit metabolism of **midazolam** (increased plasma concentration with increased sedation); absorption of lercanidipine increased by **midazolam**; diltiazem and verapamil increase plasma concentration of **buspiron** (reduce dose of buspiron)
- Aprepitant: plasma concentration of both drugs may increase when diltiazem given with **aprepitant**
- Beta-blockers: enhanced hypotensive effect when calcium-channel blockers given with **beta-blockers**; increased risk of AV block and bradycardia when diltiazem given with **beta-blockers**; asystole, severe hypotension and heart failure when verapamil given with **beta-blockers** (see p. 107); possible severe hypotension and heart failure when nifedipine given with **beta-blockers**
- Calcium-channel Blockers: plasma concentration of both drugs may increase when diltiazem given with **nifedipine**
- Cardiac Glycosides: verapamil increases plasma concentration of **digoxin**, also increased risk of AV block and bradycardia; diltiazem, lercanidipine and nicardipine increase plasma concentration of **digoxin**; nifedipine possibly increases plasma concentration of **digoxin**
- Ciclosporin: diltiazem, nicardipine and verapamil increase plasma concentration of **ciclosporin**; combination of lercanidipine with **ciclosporin** may increase plasma concentration of either drug (or both)—avoid concomitant use; plasma concentration of nifedipine possibly increased by **ciclosporin** (increased risk of toxicity including gingival hyperplasia)
- Cilostazol: diltiazem increases plasma concentration of **cilostazol** (consider reducing dose of cilostazol)
- Clonidine: enhanced hypotensive effect when calcium-channel blockers given with **clonidine**
- Colchicine: diltiazem and verapamil possibly increase risk of **colchicine** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: hypotensive effect of calcium-channel blockers antagonised by **corticosteroids**; diltiazem increases plasma concentration of **methylprednisolone**
- Cytotoxics: verapamil possibly increases plasma concentration of **doxorubicin**; verapamil possibly increases the plasma concentration of **afatinib**—manufacturer of afatinib advises separating administration of verapamil by 6 to 12 hours; diltiazem and verapamil possibly increase the plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosuti-

Calcium-channel Blockers● Cytotoxics (*continued*)

nib; possible increased risk of bradycardia when diltiazem or verapamil given with **crizotinib**; plasma concentration of both drugs may increase when verapamil given with **everolimus** (consider reducing the dose of everolimus—consult everolimus product literature); nifedipine possibly inhibits metabolism of **vincristine**

Dapoxetine: manufacturer of dapoxetine advises dose reduction when diltiazem and verapamil given with **dapoxetine** (see Dose under Dapoxetine, BNF section 7.4.6)

Diazoxide: enhanced hypotensive effect when calcium-channel blockers given with **diazoxide**

Diuretics: enhanced hypotensive effect when calcium-channel blockers given with **diuretics**; diltiazem and verapamil increase plasma concentration of **eplerenone** (reduce dose of eplerenone)

Dopaminergics: enhanced hypotensive effect when calcium-channel blockers given with **levodopa**

Fidaxomicin: avoidance of verapamil advised by manufacturer of **fidaxomicin**

● Fingolimod: possible increased risk of bradycardia when diltiazem or verapamil given with **fingolimod**

Grapefruit Juice: plasma concentration of felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil increased by **grapefruit juice**; plasma concentration of amlodipine possibly increased by **grapefruit juice**

Hormone Antagonists: diltiazem and verapamil increase plasma concentration of **datusteride**; possible increased risk of bradycardia when diltiazem or verapamil given with **pasireotide**

● Ivabradine: diltiazem and verapamil increase plasma concentration of **ivabradine**—avoid concomitant use● Lenalidomide: verapamil possibly increases plasma concentration of **lenalidomide** (increased risk of toxicity)● Lipid-regulating Drugs: diltiazem increases plasma concentration of **atorvastatin**—possible increased risk of myopathy; possible increased risk of myopathy when amlodipine and diltiazem given with **simvastatin** (see Dose under Simvastatin, p. 126); increased risk of myopathy when verapamil given with **simvastatin** (see Dose under Simvastatin, p. 126); avoidance of diltiazem and verapamil advised by manufacturer of **lomitapide** (plasma concentration of lomitapide possibly increased)

Lithium: neurotoxicity may occur when diltiazem or verapamil given with **lithium** without increased plasma concentration of lithium

● Magnesium (parenteral): profound hypotension reported with concomitant use of nifedipine and **parenteral magnesium** in pre-eclampsia

Methyldopa: enhanced hypotensive effect when calcium-channel blockers given with **methyldopa**

Moxisylyte: enhanced hypotensive effect when calcium-channel blockers given with **moxisylyte**

Moxonidine: enhanced hypotensive effect when calcium-channel blockers given with **moxonidine**

Muscle Relaxants: verapamil enhances effects of **non-depolarising muscle relaxants** and **suxamethonium**; enhanced hypotensive effect when calcium-channel blockers given with **baclofen** or **tizanidine**; manufacturer of verapamil advises avoid concomitant use of **intravenous dantrolene**; possible increased risk of ventricular arrhythmias when diltiazem given with **intravenous dantrolene**—manufacturer of diltiazem advises avoid concomitant use; calcium-channel blockers possibly enhance effects of **non-depolarising muscle relaxants**

Nitrates: enhanced hypotensive effect when calcium-channel blockers given with **nitrates**

Calcium-channel Blockers (*continued*)

Oestrogens: hypotensive effect of calcium-channel blockers antagonised by **oestrogens**

Prostaglandins: enhanced hypotensive effect when calcium-channel blockers given with **alprostadil**

Ranolazine: diltiazem and verapamil increase plasma concentration of **ranolazine** (consider reducing dose of ranolazine)

Sildenafil: enhanced hypotensive effect when amlodipine given with **sildenafil**

● Sirolimus: diltiazem increases plasma concentration of **sirolimus**; plasma concentration of both drugs increased when verapamil given with **sirolimus**

Sulfapyrazone: plasma concentration of verapamil reduced by **sulfapyrazone**

● Tacrolimus: diltiazem and nifedipine increase plasma concentration of **tacrolimus**; felodipine, nicardipine and verapamil possibly increase plasma concentration of **tacrolimus**● Theophylline: calcium-channel blockers possibly increase plasma concentration of **theophylline** (enhanced effect); diltiazem increases plasma concentration of **theophylline**; verapamil increases plasma concentration of **theophylline** (enhanced effect)

Ticagrelor: diltiazem increases plasma concentration of **ticagrelor**

Ulcer-healing Drugs: metabolism of calcium-channel blockers possibly inhibited by **cimetidine** (increased plasma concentration)

Ulipristal: avoidance of verapamil advised by manufacturer of **ulipristal**

Vardenafil: enhanced hypotensive effect when nifedipine given with **vardenafil**

Vasodilator Antihypertensives: enhanced hypotensive effect when calcium-channel blockers given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Calcium-channel Blockers (dihydropyridines) *see* Calcium-channel Blockers**Canagliflozin** *see* Antidiabetics**Candesartan** *see* Angiotensin-II Receptor Antagonists**Cannabis Extract**

Antidepressants: possible increased risk of hypertension and tachycardia when cannabis extract given with **tricyclics**

Capecitabine *see* Fluorouracil**Capreomycin**

Antibacterials: increased risk of nephrotoxicity when capreomycin given with **colistimethate sodium** or **polymyxins**; increased risk of nephrotoxicity and ototoxicity when capreomycin given with **aminoglycosides** or **vancomycin**

Cytotoxics: increased risk of nephrotoxicity and ototoxicity when capreomycin given with **platinum compounds**

Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Captopril *see* ACE Inhibitors**Carbamazepine**

Alcohol: CNS side-effects of carbamazepine possibly increased by **alcohol**

● Analgesics: effects of carbamazepine enhanced by **dextropropoxyphene**; carbamazepine possibly accelerates metabolism of **fentanyl** (reduced effect); carbamazepine reduces plasma concentration of **methadone**; carbamazepine reduces effects of **tramadol**; carbamazepine possibly accelerates metabolism of **paracetamol** (also isolated reports of hepatotoxicity)● Anti-arrhythmics: carbamazepine possibly reduces plasma concentration of **dronedronone**—avoid concomitant use● Antibacterials: plasma concentration of carbamazepine increased by **clarithromycin** (consider reducing dose of carbamazepine); plasma concentration of carbamazepine increased by **erythromycin**;

Carbamazepine

- **Antibacterials** (*continued*)
plasma concentration of carbamazepine reduced by ●**rifabutin**; carbamazepine accelerates metabolism of ●**doxycycline** (reduced effect); plasma concentration of carbamazepine increased by ●**isoniazid** (also possibly increased isoniazid hepatotoxicity); carbamazepine reduces plasma concentration of ●**telithromycin** (avoid during and for 2 weeks after carbamazepine)
- **Anticoagulants**: carbamazepine accelerates metabolism of ●**coumarins** (reduced anticoagulant effect); carbamazepine possibly reduces plasma concentration of ●**dabigatran**—manufacturer of dabigatran advises avoid concomitant use; carbamazepine possibly reduces plasma concentration of ●**rivaroxaban**—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- **Antidepressants**: carbamazepine possibly reduces plasma concentration of ●**reboxetine**; plasma concentration of carbamazepine increased by ●**fluoxetine** and ●**fluvoxamine**; carbamazepine reduces plasma concentration of ●**mianserin**, ●**mirtazapine** and ●**trazodone**; manufacturer of carbamazepine advises avoid for 2 weeks after stopping ●**MAOIs**, also antagonism of anticonvulsant effect; anticonvulsant effect of antiepileptics possibly antagonised by ●**MAOIs** and ●**tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by ●**SSRIs** and ●**tricyclics** (convulsive threshold lowered); plasma concentration of carbamazepine possibly reduced by ●**St John's wort**; carbamazepine accelerates metabolism of ●**tricyclics** (reduced plasma concentration and reduced effect)
- **Antiepileptics**: carbamazepine possibly reduces plasma concentration of ●**eslicarbazepine** but risk of side-effects increased; carbamazepine possibly reduces plasma concentration of ●**ethosuximide** and ●**retigabine**; carbamazepine often reduces plasma concentration of ●**lamotrigine**, also plasma concentration of an active metabolite of carbamazepine sometimes raised (but evidence is conflicting); possible increased risk of carbamazepine toxicity when given with ●**levetiracetam**; plasma concentration of carbamazepine sometimes reduced by ●**oxcarbazepine** (but concentration of an active metabolite of carbamazepine may be increased), also plasma concentration of an active metabolite of oxcarbazepine often reduced; carbamazepine reduces plasma concentration of ●**perampanel** (see Dose under Perampanel, p. 226); carbamazepine possibly increases plasma concentration of ●**phenobarbital**; plasma concentration of both drugs often reduced when carbamazepine given with ●**phenytoin**, also plasma concentration of phenytoin may be increased; plasma concentration of both drugs possibly reduced when carbamazepine given with ●**rufinamide**; plasma concentration of carbamazepine increased by ●**stiripentol**; carbamazepine reduces plasma concentration of ●**tiagabine** and ●**zonisamide**; carbamazepine often reduces plasma concentration of ●**topiramate**; carbamazepine reduces plasma concentration of ●**valproate**, also plasma concentration of active metabolite of carbamazepine increased
- **Antifungals**: plasma concentration of carbamazepine possibly increased by ●**fluconazole** and ●**micronazole**; carbamazepine possibly reduces plasma concentration of ●**itraconazole** and ●**posaconazole**; carbamazepine possibly reduces plasma concentration of ●**voriconazole**—avoid concomitant use; carbamazepine possibly reduces plasma concentration of ●**caspofungin**—consider increasing dose of caspofungin
- **Antimalarials**: avoidance of carbamazepine advised by manufacturer of ●**piperazine with arteminol**;

Carbamazepine

- **Antimalarials** (*continued*)
anticonvulsant effect of antiepileptics antagonised by ●**mefloquine**
- **Antipsychotics**: anticonvulsant effect of antiepileptics antagonised by ●**antipsychotics** (convulsive threshold lowered); carbamazepine accelerates metabolism of ●**haloperidol**, ●**olanzapine**, ●**quetiapine** and ●**risperidone** (reduced plasma concentration); carbamazepine reduces plasma concentration of ●**aripiprazole** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); carbamazepine accelerates metabolism of ●**clozapine** (reduced plasma concentration), also avoid concomitant use of drugs with substantial potential for causing agranulocytosis; carbamazepine reduces plasma concentration of ●**paliperidone**
- **Antivirals**: avoidance of carbamazepine advised by manufacturer of ●**boceprevir** and ●**rilpivirine** (plasma concentration of boceprevir and rilpivirine possibly reduced); carbamazepine possibly reduces plasma concentration of ●**darunavir**, ●**fosamprenavir**, ●**lopinavir**, ●**sagunavir** and ●**tipranavir**; avoidance of carbamazepine advised by manufacturer of ●**dolutegravir**, ●**elvitegravir**, ●**etravirine**, ●**sofosbuvir** and ●**telaprevir**; plasma concentration of both drugs reduced when carbamazepine given with ●**efavirenz**; carbamazepine possibly reduces plasma concentration of ●**indinavir**, also plasma concentration of carbamazepine possibly increased; carbamazepine reduces plasma concentration of ●**nevirapine**; plasma concentration of carbamazepine possibly increased by ●**ritonavir**
- **Anxiolytics and Hypnotics**: carbamazepine often reduces plasma concentration of ●**clonazepam**; carbamazepine reduces plasma concentration of ●**midazolam**
- **Appetitant**: carbamazepine possibly reduces plasma concentration of ●**aprepitant**
- **Bupropion**: carbamazepine reduces plasma concentration of ●**bupropion**
- **Calcium-channel Blockers**: carbamazepine reduces effects of ●**felodipine**; carbamazepine probably reduces effects of ●**dihydropyridines**, ●**nifedipine** and ●**nifedipine**; avoidance of carbamazepine advised by manufacturer of ●**nimodipine** (plasma concentration of nimodipine possibly reduced); effects of carbamazepine enhanced by ●**diltiazem** and ●**verapamil**
- **Ciclosporin**: carbamazepine accelerates metabolism of ●**ciclosporin** (reduced plasma concentration)
- **Clopidogrel**: carbamazepine possibly reduces antiplatelet effect of ●**clopidogrel**
- **Cobicistat**: carbamazepine possibly reduces plasma concentration of ●**cobicistat**—manufacturer of cobicistat advises avoid concomitant use
- **Corticosteroids**: carbamazepine accelerates metabolism of ●**corticosteroids** (reduced effect)
- **Cytotoxics**: carbamazepine possibly decreases plasma concentration of ●**axitinib** (increase dose of axitinib—consult axitinib product literature); carbamazepine possibly reduces plasma concentration of ●**bosutinib** and ●**crizotinib**—manufacturer of bosutinib and crizotinib advises avoid concomitant use; avoidance of carbamazepine advised by manufacturer of ●**cabazitaxel**, ●**dabrafenib**, ●**gefitinib** and ●**vemurafenib**; carbamazepine reduces plasma concentration of ●**imatinib** and ●**lapatinib**—avoid concomitant use; avoidance of carbamazepine advised by manufacturer of ●**vandetanib** and ●**vismodegib** (plasma concentration of vandetanib and vismodegib possibly reduced); carbamazepine possibly reduces plasma concentration of ●**eribulin**; carbamazepine reduces plasma concentration of ●**irinotecan** and its active metabolite; manufacturer of procarbazine advises possible increased risk of

Carbamazepine

- Cytotoxics (*continued*)
hypersensitivity reactions when carbamazepine given with **procarbazine**
- Diuretics: increased risk of hyponatraemia when carbamazepine given with **diuretics**; plasma concentration of carbamazepine increased by **acetazolamide**; carbamazepine reduces plasma concentration of **eplerenone**—avoid concomitant use
- Hormone Antagonists: carbamazepine possibly reduces plasma concentration of **abiraterone**—manufacturer of abiraterone advises avoid concomitant use; metabolism of carbamazepine inhibited by **danazol** (increased risk of toxicity); carbamazepine possibly accelerates metabolism of **toremifene** (reduced plasma concentration)
- 5HT₂-receptor Antagonists: carbamazepine accelerates metabolism of **ondansetron** (reduced effect)
- Ivacaftor: carbamazepine possibly reduces plasma concentration of **ivacaftor**—manufacturer of ivacaftor advises avoid concomitant use
- Lipid-regulating Drugs: carbamazepine reduces plasma concentration of **simvastatin**—consider increasing dose of simvastatin
- Lithium: neurotoxicity may occur when carbamazepine given with **lithium** without increased plasma concentration of lithium
- Macitentan: avoidance of carbamazepine advised by manufacturer of **macitentan**
- Muscle Relaxants: carbamazepine antagonises muscle relaxant effect of **non-depolarising muscle relaxants** (accelerated recovery from neuromuscular blockade)
- Oestrogens: carbamazepine accelerates metabolism of **oestrogens** (reduced contraceptive effect—see p. 402)
- Orlistat: possible increased risk of convulsions when antiepileptics given with **orlistat**
- Progestogens: carbamazepine accelerates metabolism of **progestogens** (reduced contraceptive effect—see p. 402)
- Retinoids: plasma concentration of carbamazepine possibly reduced by **isotretinoin**
- Roflumilast: carbamazepine possibly inhibits effects of **roflumilast** (manufacturer of roflumilast advises avoid concomitant use)
- Theophylline: carbamazepine accelerates metabolism of **theophylline** (reduced effect)
- Thyroid Hormones: carbamazepine accelerates metabolism of **thyroid hormones** (may increase requirements for thyroid hormones in hypothyroidism)
- Tibolone: carbamazepine accelerates metabolism of **tibolone** (reduced plasma concentration)
- Ticagrelor: carbamazepine possibly reduces plasma concentration of **ticagrelor**
- Ulcer-healing Drugs: metabolism of carbamazepine inhibited by **cimetidine** (increased plasma concentration)
- Ulipristal: avoidance of carbamazepine advised by manufacturer of **ulipristal** (contraceptive effect of ulipristal possibly reduced)
- Vitamins: carbamazepine possibly increases requirements for **vitamin D**

Carbapenems see Ertapenem, Imipenem with Cilastatin, and Meropenem

Carbonic Anhydrase Inhibitors see Diuretics

Carboplatin see Platinum Compounds

Carboprost see Prostaglandins

Cardiac Glycosides

- ACE Inhibitors: plasma concentration of digoxin possibly increased by **captopril**
- Alpha-blockers: plasma concentration of digoxin increased by **prazosin**
- Aminosalicylates: absorption of digoxin possibly reduced by **sulfasalazine**

Cardiac Glycosides (*continued*)

- Analgesics: plasma concentration of cardiac glycosides possibly increased by **NSAIDs**, also possible exacerbation of heart failure and reduction of renal function
- Antacids: absorption of digoxin possibly reduced by **antacids**
- Anti-arrhythmics: plasma concentration of digoxin increased by **amiodarone**, **dronedarone** and **propafenone** (halve dose of digoxin)
- Antibacterials: plasma concentration of digoxin possibly increased by **gentamicin**, **telithromycin** and **trimethoprim**; absorption of digoxin reduced by **neomycin**; plasma concentration of digoxin possibly reduced by **rifampicin**; plasma concentration of digoxin increased by **macrolides** (increased risk of toxicity)
- Antidepressants: plasma concentration of digoxin reduced by **St John's wort**—avoid concomitant use
- Antidiabetics: plasma concentration of digoxin possibly reduced by **acarbose**; plasma concentration of digoxin increased by **canagliflozin** and **sitagliptin**
- Antiepileptics: plasma concentration of digoxin possibly reduced by **phenytoin**
- Antifungals: increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with **amphotericin**; plasma concentration of digoxin increased by **itraconazole**
- Antimalarials: plasma concentration of digoxin possibly increased by **chloroquine** and **hydroxychloroquine**; possible increased risk of bradycardia when digoxin given with **mefloquine**; plasma concentration of digoxin increased by **quinine**
- Antimuscarinics: plasma concentration of digoxin possibly increased by **darifenacin**
- Antivirals: side-effects of digoxin possibly increased by **bocoprevir**; plasma concentration of digoxin increased by **etravirine** and **telaprevir**; plasma concentration of digoxin possibly increased by **ritonavir**
- Anxiolytics and Hypnotics: plasma concentration of digoxin increased by **alprazolam** (increased risk of toxicity)
- Beta-blockers: increased risk of AV block and bradycardia when cardiac glycosides given with **beta-blockers**
- Calcium Salts: arrhythmias can be precipitated when cardiac glycosides given with large **intravenous** doses of **calcium salts**
- Calcium-channel Blockers: plasma concentration of digoxin increased by **diltiazem**, **flercanidipine** and **nicardipine**; plasma concentration of digoxin possibly increased by **nifedipine**; plasma concentration of digoxin increased by **verapamil**, also increased risk of AV block and bradycardia
- Ciclosporin: plasma concentration of digoxin increased by **ciclosporin** (increased risk of toxicity)
- Cobicistat: plasma concentration of digoxin possibly increased by **cobicistat**—reduce initial dose of digoxin
- Colchicine: possible increased risk of myopathy when digoxin given with **colchicine**
- Corticosteroids: increased risk of hypokalaemia when cardiac glycosides given with **corticosteroids**
- Cytotoxics: absorption of digoxin **tablets** possibly reduced by **bleomycin**, **carmustine**, **cyclophosphamide**, **cytarabine**, **doxorubicin**, **melfalan**, **methotrexate**, **procarbazine** and **vincristine**; possible increased risk of bradycardia when digoxin given with **crizotinib**; plasma concentration of digoxin increased by **vandetanib**—possible increased risk of bradycardia
- Diuretics: increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with **acetazolamide**, **loop diuretics** or **thiazides and related diuretics**; plasma concentration of digoxin

Cardiac Glycosides

- Diuretics (*continued*)
 - possibly increased by **potassium canrenoate**;
 - plasma concentration of digoxin increased by
 - **spironolactone**
- Lenalidomide: plasma concentration of digoxin possibly increased by **lenalidomide**
- Lipid-regulating Drugs: absorption of cardiac glycosides possibly reduced by **colestipol** and **colestyramine**; plasma concentration of digoxin possibly increased by **atorvastatin**
- Mirabegron: plasma concentration of digoxin increased by **mirabegron**—reduce initial dose of digoxin
- Muscle Relaxants: risk of ventricular arrhythmias when cardiac glycosides given with **suxamethonium**; possible increased risk of bradycardia when cardiac glycosides given with **tizanidine**
- Penicillamine: plasma concentration of digoxin possibly reduced by **penicillamine**
- Ranolazine: plasma concentration of digoxin increased by **ranolazine**
- Sympathomimetics, Beta₂: plasma concentration of digoxin possibly reduced by **salbutamol**
- Ticagrelor: plasma concentration of digoxin increased by **ticagrelor**
- Tolvaptan: plasma concentration of digoxin increased by **tolvaptan** (increased risk of toxicity)
- Ulcer-healing Drugs: plasma concentration of digoxin possibly slightly increased by **proton pump inhibitors**; absorption of cardiac glycosides possibly reduced by **sucralfate**
- Ulipristal: manufacturer of ulipristal advises give digoxin at least 1.5 hours before or after **ulipristal**

Carmustine

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Cardiac Glycosides: carmustine possibly reduces absorption of **digoxin tablets**
- Ulcer-healing Drugs: myelosuppressive effects of carmustine possibly enhanced by **cimetidine**

Carotolol *see* Beta-blockers**Carvedilol** *see* Beta-blockers**Caspofungin**

- Antibacterials: plasma concentration of caspofungin initially increased and then reduced by **rifampicin** (consider increasing dose of caspofungin)
- Antiepileptics: plasma concentration of caspofungin possibly reduced by **carbamazepine** and **phenytoin**—consider increasing dose of caspofungin
- Antivirals: plasma concentration of caspofungin possibly reduced by **efavirenz** and **nevirapine**—consider increasing dose of caspofungin
- Ciclosporin: plasma concentration of caspofungin increased by **ciclosporin** (manufacturer of caspofungin recommends monitoring liver enzymes)
- Corticosteroids: plasma concentration of caspofungin possibly reduced by **dexamethasone**—consider increasing dose of caspofungin
- Tacrolimus: caspofungin reduces plasma concentration of **tacrolimus**

Cefaclor *see* Cephalosporins**Cefadroxil** *see* Cephalosporins**Cefalexin** *see* Cephalosporins**Cefixime** *see* Cephalosporins**Cefotaxime** *see* Cephalosporins**Cefradine** *see* Cephalosporins**Ceftaroline** *see* Cephalosporins**Ceftazidime** *see* Cephalosporins**Ceftriaxone** *see* Cephalosporins**Cefuroxime** *see* Cephalosporins**Celecoxib** *see* NSAIDs**Celiprolol** *see* Beta-blockers**Cephalosporins**

Antacids: absorption of cefaclor reduced by **antacids**

Cephalosporins (*continued*)

- Antibacterials: possible increased risk of nephrotoxicity when cephalosporins given with **aminoglycosides**
- Anticoagulants: cephalosporins possibly enhance anticoagulant effect of **coumarins**
- Probenecid: excretion of cephalosporins reduced by **probenecid** (increased plasma concentration)
- Teriflunomide: plasma concentration of cefaclor increased by **teriflunomide**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Certolizumab pegol

- Abatacept: avoid concomitant use of certolizumab pegol with **abatacept**
- Anakinra: avoid concomitant use of certolizumab pegol with **anakinra**
- Vaccines: avoid concomitant use of certolizumab pegol with live **vaccines** (*see* p. 604)

Cetirizine *see* Antihistamines**Chenodeoxycholic Acid** *see* Bile Acids**Chloral** *see* Anxiolytics and Hypnotics**Chloramphenicol**

- Antibacterials: metabolism of chloramphenicol accelerated by **rifampicin** (reduced plasma concentration)
- Anticoagulants: chloramphenicol enhances anticoagulant effect of **coumarins**
- Antidiabetics: chloramphenicol enhances effects of **sulfonylureas**
- Antiepileptics: metabolism of chloramphenicol possibly accelerated by **phenobarbital** (reduced plasma concentration); chloramphenicol increases plasma concentration of **phenytoin** (increased risk of toxicity)
- Antipsychotics: avoid concomitant use of chloramphenicol with **clozapine** (increased risk of agranulocytosis)
- Ciclosporin: chloramphenicol possibly increases plasma concentration of **ciclosporin**
- Clopidogrel: chloramphenicol possibly reduces antiplatelet effect of **clopidogrel**
- Hydroxocobalamin: chloramphenicol reduces response to **hydroxocobalamin**
- Tacrolimus: chloramphenicol possibly increases plasma concentration of **tacrolimus**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Chlordiazepoxide *see* Anxiolytics and Hypnotics**Chloroprocaine**

- Antibacterials: chloroprocaine possibly inhibits effects of **sulfonamides** (manufacturer of chloroprocaine advises avoid concomitant use)

Chloroquine and Hydroxychloroquine

- Adsorbents: absorption of chloroquine and hydroxychloroquine reduced by **kaolin**
- Agalsidase Alfa and Beta: chloroquine and hydroxychloroquine possibly inhibit effects of **agalsidase alfa and beta** (manufacturers of agalsidase alfa and beta advise avoid concomitant use)
- Antacids: absorption of chloroquine and hydroxychloroquine reduced by **antacids**
- Anti-arrhythmics: increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with **amiodarone**—avoid concomitant use
- Antibacterials: increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with **moxifloxacin**—avoid concomitant use
- Antidepressants: avoidance of antimalarials advised by manufacturer of **citalopram** and **escitalopram** (risk of ventricular arrhythmias)
- Antimalarials: avoidance of antimalarials advised by manufacturer of **artemether with lumefantrine**; increased risk of convulsions when chloroquine and hydroxychloroquine given with **mefloquine**

Chloroquine and Hydroxychloroquine (*continued*)

- Antipsychotics: increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with **●droperidol**—avoid concomitant use
- Cardiac Glycosides: chloroquine and hydroxychloroquine possibly increase plasma concentration of **●digoxin**
- Ciclosporin: chloroquine and hydroxychloroquine increase plasma concentration of **●ciclosporin** (increased risk of toxicity)
- Cytotoxics: possible increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with **●bosutinib**
- Histamine: avoidance of antimalarials advised by manufacturer of **histamine**
- Lanthanum: absorption of chloroquine and hydroxychloroquine possibly reduced by **lanthanum** (give at least 2 hours apart)
- Larionidase: chloroquine and hydroxychloroquine possibly inhibit effects of **larionidase** (manufacturer of larionidase advises avoid concomitant use)
- Parasympathomimetics: chloroquine and hydroxychloroquine have potential to increase symptoms of myasthenia gravis and thus diminish effect of **neostigmine** and **pyridostigmine**
- Ulcer-healing Drugs: metabolism of chloroquine and hydroxychloroquine inhibited by **cimetidine** (increased plasma concentration)
- Vaccines: antimalarials inactivate **oral typhoid vaccine**—see p. 626

Chlorothiazide *see* Diuretics**Chlorphenamine** *see* Antihistamines**Chlorpromazine** *see* Antipsychotics**Chlortalidon** *see* Diuretics**Ciclesonide** *see* Corticosteroids**Ciclosporin**

- ACE Inhibitors: increased risk of hyperkalaemia when ciclosporin given with **●ACE inhibitors**
- Aliskiren: ciclosporin increases plasma concentration of **●aliskiren**—avoid concomitant use
- Allopurinol: plasma concentration of ciclosporin possibly increased by **allopurinol** (risk of nephrotoxicity)
- Ambrisentan: ciclosporin increases plasma concentration of **●ambrisentan** (see Dose under Ambrisentan, BNF section 2.5.1)
- Analgesics: increased risk of nephrotoxicity when ciclosporin given with **●NSAIDs**; ciclosporin increases plasma concentration of **●diclofenac** (halve dose of diclofenac)
- Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when ciclosporin given with **●angiotensin-II receptor antagonists**
- Anti-arrhythmic: plasma concentration of ciclosporin possibly increased by **amiodarone** and **propafenone**
- Antibacterials: metabolism of ciclosporin inhibited by **●clarithromycin** and **●erythromycin** (increased plasma concentration); metabolism of ciclosporin accelerated by **●rifampicin** (reduced plasma concentration); plasma concentration of ciclosporin possibly reduced by **●sulfadiazine**; increased risk of nephrotoxicity when ciclosporin given with **●aminoglycosides**, **●polymyxins**, **●quinolones**, **●sulfonamides** or **●vancomycin**; plasma concentration of ciclosporin possibly increased by **●chloramphenicol** and **●telithromycin**; increased risk of myopathy when ciclosporin given with **●daptomycin** (preferably avoid concomitant use); metabolism of ciclosporin possibly inhibited by **●macrolides** (increased plasma concentration); increased risk of nephrotoxicity when ciclosporin given with **●trimethoprim**, also plasma concentration of ciclosporin reduced by *intravenous* trimethoprim
- Anticoagulants: ciclosporin possibly increases plasma concentration of **●dabigatran**—manufacturer of dabigatran advises avoid concomitant use

Ciclosporin (*continued*)

- Antidepressants: plasma concentration of ciclosporin reduced by **●St John's wort**—avoid concomitant use
- Antidiabetics: ciclosporin possibly enhances hypoglycaemic effect of **repaglinide**
- Antiepileptics: metabolism of ciclosporin accelerated by **●carbamazepine**, **●phenobarbital** and **●phenytoin** (reduced plasma concentration); plasma concentration of ciclosporin possibly reduced by **oxcarbazepine**
- Antifungals: metabolism of ciclosporin possibly inhibited by **●miconazole** (increased plasma concentration); increased risk of nephrotoxicity when ciclosporin given with **●amphotericin**; metabolism of ciclosporin inhibited by **●fluconazole**, **●itraconazole**, **●posaconazole** and **●voriconazole** (increased plasma concentration); ciclosporin increases plasma concentration of **●caspofungin** (manufacturer of caspofungin recommends monitoring liver enzymes); plasma concentration of ciclosporin possibly reduced by **griseofulvin** and **terbinafine**; plasma concentration of ciclosporin possibly increased by **miconazole**
- Antimalarials: plasma concentration of ciclosporin increased by **●chloroquine and hydroxychloroquine** (increased risk of toxicity)
- Antimuscarinics: avoidance of ciclosporin advised by manufacturer of **darifenacin**
- Antivirals: increased risk of nephrotoxicity when ciclosporin given with **●acyclovir**; plasma concentration of ciclosporin possibly increased by **●atazanavir** and **●ritonavir**; plasma concentration of ciclosporin increased by **●boceprevir**, **●fosamprenavir** and **●indinavir**; plasma concentration of ciclosporin possibly reduced by **●efavirenz**; plasma concentration of both drugs increased when ciclosporin given with **●saquinavir**; plasma concentration of both drugs increased when ciclosporin given with **●telaprevir** (reduce dose of ciclosporin)
- Beta-blockers: plasma concentration of ciclosporin increased by **●carvedilol**
- Bile Acids: absorption of ciclosporin increased by **●ursodeoxycholic acid**
- Bosentan: ciclosporin increases plasma concentration of **●bosentan** (also plasma concentration of ciclosporin reduced—avoid concomitant use)
- Calcium-channel Blockers: combination of ciclosporin with **●lercanidipine** may increase plasma concentration of either drug (or both)—avoid concomitant use; plasma concentration of ciclosporin increased by **●diltiazem**, **●nicardipine** and **●verapamil**; ciclosporin possibly increases plasma concentration of **nifedipine** (increased risk of toxicity including gingival hyperplasia)
- Cardiac Glycosides: ciclosporin increases plasma concentration of **●digoxin** (increased risk of toxicity)
- Colchicine: possible increased risk of nephrotoxicity and myotoxicity when ciclosporin given with **●colchicine**—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Colestilan: manufacturer of colestilan advises give ciclosporin at least 1 hour before or 3 hours after **colestilan**
- Corticosteroids: plasma concentration of ciclosporin increased by high-dose **●methylprednisolone** (risk of convulsions); ciclosporin increases plasma concentration of **prednisolone**
- Cytotoxics: increased risk of nephrotoxicity when ciclosporin given with **●melphalan**; increased risk of neurotoxicity when ciclosporin given with **●doxorubicin**; ciclosporin increases plasma concentration of **●epirubicin** and **●idarubicin**; ciclosporin reduces excretion of **mitoxantrone** (increased plasma concentration); risk of toxicity when ciclosporin given

Ciclosporin

- **Cytotoxics (continued)**
 - with **methotrexate**; ciclosporin possibly increases the plasma concentration of **afatinib**—manufacturer of afatinib advises separating administration of ciclosporin by 6 to 12 hours; caution with ciclosporin advised by manufacturer of **crizotinib**; ciclosporin increases plasma concentration of **everolimus** (consider reducing the dose of everolimus—consult everolimus product literature); plasma concentration of ciclosporin possibly increased by **imatinib**; *in vitro* studies suggest a possible interaction between ciclosporin and **docetaxel** (consult docetaxel product literature); ciclosporin possibly increases plasma concentration of **etoposide** (increased risk of toxicity)
- **Diuretics**: plasma concentration of ciclosporin possibly increased by **acetazolamide**; increased risk of hyperkalaemia when ciclosporin given with **potassium-sparing diuretics** and **aldosterone antagonists**; increased risk of nephrotoxicity and possibly hypermagnesaemia when ciclosporin given with **thiazides** and **related diuretics**
- **Fidaxomicin**: avoidance of ciclosporin advised by manufacturer of **fidaxomicin**
- **Grapefruit Juice**: plasma concentration of ciclosporin increased by **grapefruit juice** (increased risk of toxicity)
- **Hormone Antagonists**: metabolism of ciclosporin inhibited by **danazol** (increased plasma concentration); plasma concentration of ciclosporin reduced by **lanreotide** and **octreotide**; plasma concentration of ciclosporin possibly reduced by **pasireotide**
- **Lenalidomide**: ciclosporin possibly increases plasma concentration of **lenalidomide** (increased risk of toxicity)
- **Lipid-regulating Drugs**: absorption of ciclosporin reduced by **colesevelam**; increased risk of renal impairment when ciclosporin given with **bezafibrate** or **fenofibrate**; increased risk of myopathy when ciclosporin given with **atorvastatin** (see Dose under Atorvastatin, p. 125); increased risk of myopathy when ciclosporin given with **fluvastatin** or **pravastatin**; increased risk of myopathy when ciclosporin given with **rosuvastatin** or **simvastatin** (avoid concomitant use); plasma concentration of both drugs may increase when ciclosporin given with **ezetimibe**
- **Mannitol**: possible increased risk of nephrotoxicity when ciclosporin given with **mannitol**
- **Metoclopramide**: plasma concentration of ciclosporin increased by **metoclopramide**
- **Mifamurtide**: avoidance of ciclosporin advised by manufacturer of **mifamurtide**
- **Modafinil**: plasma concentration of ciclosporin reduced by **modafinil**
- **Oestrogens**: plasma concentration of ciclosporin possibly increased by **oestrogens**
- **Orlistat**: absorption of ciclosporin possibly reduced by **orlistat**
- **Potassium Salts**: increased risk of hyperkalaemia when ciclosporin given with **potassium salts**
- **Progestogens**: plasma concentration of ciclosporin possibly increased by **progestogens**
- **Ranolazine**: plasma concentration of both drugs may increase when ciclosporin given with **ranolazine**
- **Sevelamer**: plasma concentration of ciclosporin possibly reduced by **sevelamer**
- **Sirolimus**: ciclosporin increases plasma concentration of **sirolimus**
- **Sulfinpyrazone**: plasma concentration of ciclosporin reduced by **sulfinpyrazone**
- **Tacrolimus**: plasma concentration of ciclosporin increased by **tacrolimus** (increased risk of nephrotoxicity)—avoid concomitant use

Ciclosporin (continued)

Ticagrelor: ciclosporin increases plasma concentration of **ticagrelor**

- **Ulcer-healing Drugs**: plasma concentration of ciclosporin possibly increased by **cimetidine**; plasma concentration of ciclosporin possibly affected by **omeprazole**

Vitamins: plasma concentration of ciclosporin possibly affected by **vitamin E**

Cidofovir

- **Antivirals**: manufacturers advise avoid concomitant use of cidofovir with **tenofovir**

Cilazapril see ACE Inhibitors

Cilostazol

- **Anagrelide**: avoidance of cilostazol advised by manufacturer of **anagrelide**
- **Antibacterials**: plasma concentration of cilostazol possibly increased by **clarithromycin** (see Dose under Cilostazol, BNF section 2.6.4); plasma concentration of cilostazol increased by **erythromycin** (see Dose under Cilostazol, BNF section 2.6.4)
- **Antifungals**: plasma concentration of cilostazol possibly increased by **itraconazole** (see Dose under Cilostazol, BNF section 2.6.4)
- **Antivirals**: plasma concentration of cilostazol possibly increased by **boceprevir**, **ritonavir** and **telaprevir** (see Dose under Cilostazol, BNF section 2.6.4)
- **Calcium-channel Blockers**: plasma concentration of cilostazol increased by **diltiazem** (consider reducing dose of cilostazol)
- **Ulcer-healing Drugs**: plasma concentration of cilostazol increased by **omeprazole** (see Dose under Cilostazol, BNF section 2.6.4)

Cimetidine see Histamine H₂-antagonists

Cinacalcet

- **Hormone Antagonists**: cinacalcet possibly inhibits metabolism of **tamoxifen** to active metabolite (avoid concomitant use)

Cinnarizine see Antihistamines

Ciprofibrate see Fibrates

Ciprofloxacin see Quinolones

Cisatracurium see Muscle Relaxants

Cisplatin see Platinum Compounds

Citalopram see Antidepressants, SSRI

Cladribine

- **Antipsychotics**: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- **Antivirals**: avoidance of cladribine advised by manufacturer of **lamivudine**

Clarithromycin see Macrolides

Clemastine see Antihistamines

Clindamycin

- **Muscle Relaxants**: clindamycin enhances effects of **non-depolarising muscle relaxants** and **suxamethonium**

Parasympathomimetics: clindamycin antagonises effects of **neostigmine** and **pyridostigmine**

Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Clobazam see Anxiolytics and Hypnotics

Clomethiazole see Anxiolytics and Hypnotics

Clomipramine see Antidepressants, Tricyclic

Clonazepam see Anxiolytics and Hypnotics

Clonidine

ACE Inhibitors: enhanced hypotensive effect when clonidine given with **ACE inhibitors**; previous treatment with clonidine possibly delays antihypertensive effect of **captopril**

Adrenergic Neuron Blockers: enhanced hypotensive effect when clonidine given with **adrenergic neuron blockers**

Alcohol: enhanced hypotensive effect when clonidine given with **alcohol**

Aldesleukin: enhanced hypotensive effect when clonidine given with **aldesleukin**

Clonidine (*continued*)

- Alpha-blockers: enhanced hypotensive effect when clonidine given with **alpha-blockers**
- Anaesthetics, General: enhanced hypotensive effect when clonidine given with **general anaesthetics**
- Analgesics: hypotensive effect of clonidine antagonised by **NSAIDs**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when clonidine given with **angiotensin-II receptor antagonists**
- Antidepressants: enhanced hypotensive effect when clonidine given with **MAOIs**; hypotensive effect of clonidine possibly antagonised by **mirtazapine**; hypotensive effect of clonidine antagonised by **tricyclics**, also increased risk of hypertension on clonidine withdrawal
 - Antipsychotics: enhanced hypotensive effect when clonidine given with **phenothiazines**
 - Anxiolytics and Hypnotics: enhanced hypotensive effect when clonidine given with **anxiolytics and hypnotics**
 - Beta-blockers: increased risk of withdrawal hypertension when clonidine given with **beta-blockers** (withdraw beta-blockers several days before slowly withdrawing clonidine)
 - Calcium-channel Blockers: enhanced hypotensive effect when clonidine given with **calcium-channel blockers**
 - Corticosteroids: hypotensive effect of clonidine antagonised by **corticosteroids**
 - Cytotoxics: possible increased risk of bradycardia when clonidine given with **crizotinib**
 - Diazoxide: enhanced hypotensive effect when clonidine given with **diazoxide**
 - Diuretics: enhanced hypotensive effect when clonidine given with **diuretics**
 - Dopaminergics: enhanced hypotensive effect when clonidine given with **levodopa**
 - Histamine: avoidance of clonidine advised by manufacturer of **histamine**
 - Methyldopa: enhanced hypotensive effect when clonidine given with **methyldopa**
 - Moxisylyte: enhanced hypotensive effect when clonidine given with **moxisylyte**
 - Moxonidine: enhanced hypotensive effect when clonidine given with **moxonidine**
 - Muscle Relaxants: enhanced hypotensive effect when clonidine given with **baclofen** or **tizanidine**
 - Nitrates: enhanced hypotensive effect when clonidine given with **nitrates**
 - Oestrogens: hypotensive effect of clonidine antagonised by **oestrogens**
 - Prostaglandins: enhanced hypotensive effect when clonidine given with **alprostadil**
 - Sympathomimetics: possible risk of hypertension when clonidine given with **adrenaline (epinephrine)** or **noradrenaline (norepinephrine)**; serious adverse events reported with concomitant use of clonidine and **methylphenidate** (causality not established)
 - Vasodilator Antihypertensives: enhanced hypotensive effect when clonidine given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Cloпамide *see* Diuretics

Clopidogrel

- Analgesics: increased risk of bleeding when clopidogrel given with **NSAIDs** or **aspirin**
- Antibacterials: antiplatelet effect of clopidogrel possibly reduced by **chloramphenicol**, **ciprofloxacin** and **erythromycin**
 - Anticoagulants: manufacturer of clopidogrel advises avoid concomitant use with **warfarin**; antiplatelet action of clopidogrel enhances anticoagulant effect of **coumarins** and **phenindione**; increased risk of bleeding when clopidogrel given with **heparins**

Clopidogrel (*continued*)

- Antidepressants: antiplatelet effect of clopidogrel possibly reduced by **fluoxetine**, **fluvoxamine** and **moclobemide**
 - Antiepileptics: antiplatelet effect of clopidogrel possibly reduced by **carbamazepine** and **oxcarbazepine**
 - Antifungals: antiplatelet effect of clopidogrel possibly reduced by **fluconazole**, **itraconazole** and **voriconazole**
 - Antivirals: antiplatelet effect of clopidogrel possibly reduced by **etravirine**
- Dipyridamole: increased risk of bleeding when clopidogrel given with **dipyridamole**
- Iloprost: increased risk of bleeding when clopidogrel given with **iloprost**
- Prasugrel: possible increased risk of bleeding when clopidogrel given with **prasugrel**
- Ulcer-healing Drugs: antiplatelet effect of clopidogrel possibly reduced by **cimetidine**, **lansoprazole**, **pantoprazole** and **rabeprazole**; antiplatelet effect of clopidogrel reduced by **esomeprazole** and **omeprazole**
- Clozapine** *see* Antipsychotics
- Co-amoxiclav** *see* Penicillins
- Co-beneldopa** *see* Levodopa
- Cobicistat**
- Alpha-blockers: cobicistat possibly increases plasma concentration of **alfuzosin**—manufacturer of cobicistat advises avoid concomitant use
 - Anti-arrhythmics: cobicistat possibly increases plasma concentration of **amiodarone**—manufacturer of cobicistat advises avoid concomitant use
 - Antibacterials: plasma concentration of cobicistat reduced by **rifabutin** (adjust dose—consult product literature); plasma concentration of cobicistat possibly reduced by **rifampicin**—manufacturer of cobicistat advises avoid concomitant use
 - Anticoagulants: cobicistat possibly enhances anticoagulant effect of **rivaroxaban**—avoid concomitant use
 - Antidepressants: plasma concentration of cobicistat possibly reduced by **St John's wort**—manufacturer of cobicistat advises avoid concomitant use
 - Antiepileptics: plasma concentration of cobicistat possibly reduced by **carbamazepine**, **phenobarbital** and **phenytoin**—manufacturer of cobicistat advises avoid concomitant use
 - Antifungals: cobicistat possibly increases plasma concentration of **itraconazole**—manufacturer of cobicistat advises reduce dose of itraconazole
 - Antipsychotics: cobicistat possibly increases plasma concentration of **pimozide**—manufacturer of cobicistat advises avoid concomitant use
 - Antivirals: manufacturer of cobicistat advises avoid concomitant use with **boceprevir**; cobicistat possibly increases plasma concentration of **maraviroc** (reduce dose of maraviroc); avoidance of cobicistat advised by manufacturer of **nevirapine**
 - Anxiolytics and Hypnotics: manufacturer of cobicistat advises avoid concomitant use with **oral midazolam**
 - Bosentan: manufacturer of cobicistat advises avoid concomitant use with **bosentan**
 - Cardiac Glycosides: cobicistat possibly increases plasma concentration of **digoxin**—reduce initial dose of digoxin
 - Ergot Alkaloids: cobicistat possibly increases plasma concentration of **ergot alkaloids**—manufacturer of cobicistat advises avoid concomitant use
 - Lipid-regulating Drugs: cobicistat possibly increases plasma concentration of **atorvastatin**—manufacturer of cobicistat advises reduce dose of atorvastatin; manufacturer of cobicistat advises avoid concomitant use with **simvastatin**

Cobicistat (continued)

- Oestrogens: cobicistat accelerates metabolism of ●**oestrogens** (reduced contraceptive effect—see p. 402)
- Progestogens: cobicistat increases plasma concentration of ●**norgestimate**
- Sildenafil: cobicistat possibly increases plasma concentration of ●**sildenafil**—manufacturer of cobicistat advises avoid concomitant use of sildenafil for pulmonary arterial hypertension or reduce dose of sildenafil for erectile dysfunction—consult cobicistat product literature
- Sympathomimetics, Beta₂: manufacturer of cobicistat advises avoid concomitant use with ●**salmeterol**
- Tadalafil: cobicistat possibly increases plasma concentration of ●**tadalafil**—manufacturer of cobicistat advises reduce dose of tadalafil (consult cobicistat product literature)
- Vardenafil: cobicistat possibly increases plasma concentration of ●**vardenafil**—manufacturer of cobicistat advises reduce dose of vardenafil (consult cobicistat product literature)

Co-careldopa see Levodopa

Codeine see Opioid Analgesics

Co-fluampicil see Penicillins

Colchicine

- Anti-arrhythmics: possible increased risk of colchicine toxicity when given with ●**amiodarone**
- Antibacterials: possible increased risk of colchicine toxicity when given with ●**azithromycin**, ●**clarithromycin**, ●**erythromycin** and ●**tetracycline**—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Antifungals: possible increased risk of colchicine toxicity when given with ●**itraconazole**—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Antivirals: possible increased risk of colchicine toxicity when given with ●**atazanavir**, ●**indinavir**, ●**ritonavir** and ●**telaprevir**—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Calcium-channel Blockers: possible increased risk of colchicine toxicity when given with ●**diltiazem** and ●**verapamil**—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Cardiac Glycosides: possible increased risk of myopathy when colchicine given with ●**digoxin**
- Ciclosporin: possible increased risk of nephrotoxicity and myotoxicity when colchicine given with ●**ciclosporin**—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Grapefruit Juice: possible increased risk of colchicine toxicity when given with ●**grapefruit juice**
- Lipid-regulating Drugs: possible increased risk of myopathy when colchicine given with ●**fibrates** or ●**statins**

Colesevelam

Note Other drugs should be taken at least 4 hours before or after colestevlam to reduce possible interference with absorption

Antidiabetics: colestevlam reduces absorption of ●**glibenclamide** and ●**glipizide**; colestevlam reduces absorption of ●**glimepiride**—manufacturer of glimepiride advises give at least 4 hours before colestevlam; manufacturer of canagliflozin advises give bile acid sequestrants at least 1 hour after or 4–6 before ●**canagliflozin**

Antiepileptics: colestevlam possibly reduces absorption of ●**phenytoin**

- Ciclosporin: colestevlam reduces absorption of ●**ciclosporin**

Colesevelam (continued)

Lipid-regulating Drugs: bile acid sequestrants possibly reduce absorption of ●**lomitapide** (give at least 4 hours apart)

Oestrogens: colestevlam reduces absorption of ●**ethinylestradiol**

Thyroid Hormones: colestevlam reduces absorption of ●**levothyroxine**

Colestilan

Note Other drugs should be taken at least 1 hour before or 3 hours after colestilan to reduce possible interference with absorption

Ciclosporin: manufacturer of colestilan advises give ●**ciclosporin** at least 1 hour before or 3 hours after colestilan

Mycophenolate: manufacturer of colestilan advises give ●**mycophenolate** at least 1 hour before or 3 hours after colestilan

Tacrolimus: manufacturer of colestilan advises give ●**tacrolimus** at least 1 hour before or 3 hours after colestilan

Thyroid Hormones: manufacturer of colestilan advises give ●**levothyroxine** at least 1 hour before or 3 hours after colestilan

Colestipol

Note Other drugs should be taken at least 1 hour before or 4–6 hours after colestipol to reduce possible interference with absorption

Antibacterials: colestipol possibly reduces absorption of ●**tetracycline**

Antidiabetics: manufacturer of canagliflozin advises give bile acid sequestrants at least 1 hour after or 4–6 before ●**canagliflozin**

Bile Acids: colestipol possibly reduces absorption of ●**bile acids**

Cardiac Glycosides: colestipol possibly reduces absorption of ●**cardiac glycosides**

Diuretics: colestipol reduces absorption of ●**thiazides and related diuretics** (give at least 2 hours apart)

Lipid-regulating Drugs: bile acid sequestrants possibly reduce absorption of ●**lomitapide** (give at least 4 hours apart)

Thyroid Hormones: colestipol reduces absorption of ●**thyroid hormones**

Colestyramine

Note Other drugs should be taken at least 1 hour before or 4–6 hours after colestyramine to reduce possible interference with absorption

Analgesics: colestyramine increases the excretion of ●**meloxicam**; colestyramine reduces absorption of ●**paracetamol**

Antibacterials: colestyramine possibly reduces absorption of ●**tetracycline**; colestyramine antagonises effects of ●**oral vancomycin**

- Anticoagulants: colestyramine may enhance or reduce anticoagulant effect of ●**coumarins** and ●**phenindione**

Antidiabetics: colestyramine possibly enhances hypoglycaemic effect of ●**acarbose**; manufacturer of canagliflozin advises give bile acid sequestrants at least 1 hour after or 4–6 before ●**canagliflozin**

Antiepileptics: colestyramine possibly reduces absorption of ●**valproate**

Bile Acids: colestyramine possibly reduces absorption of ●**bile acids**

Cardiac Glycosides: colestyramine possibly reduces absorption of ●**cardiac glycosides**

Diuretics: colestyramine reduces absorption of ●**thiazides and related diuretics** (give at least 2 hours apart)

Leflunomide: colestyramine significantly decreases effect of ●**leflunomide** (enhanced elimination)—avoid unless drug elimination desired

Lipid-regulating Drugs: bile acid sequestrants possibly reduce absorption of ●**lomitapide** (give at least 4 hours apart)

Colestyramine (*continued*)

Mycophenolate: colestyramine reduces absorption of **mycophenolate**

Raloxifene: colestyramine reduces absorption of **raloxifene** (manufacturer of raloxifene advises avoid concomitant administration)

Teriflunomide: colestyramine significantly decreases effect of **teriflunomide** (enhanced elimination)—avoid unless drug elimination desired

Thyroid Hormones: colestyramine reduces absorption of **thyroid hormones**

Vitamins: colestyramine possibly reduces absorption of **calcitriol** (give at least 1 hour before or 4 to 6 hours after colestyramine)

Colistimethate Sodium *see* Polymyxins**Contraceptives, oral** *see* Oestrogens and Progestogens**Corticosteroids**

Note Interactions do not generally apply to corticosteroids used for topical action (including inhalation) unless specified
ACE Inhibitors: corticosteroids antagonise hypotensive effect of **ACE inhibitors**

Adrenergic Neurone Blockers: corticosteroids antagonise hypotensive effect of **adrenergic neurone blockers**

- **Aldesleukin:** avoidance of corticosteroids advised by manufacturer of **aldesleukin**

Alpha-blockers: corticosteroids antagonise hypotensive effect of **alpha-blockers**

Analgesics: increased risk of gastro-intestinal bleeding and ulceration when corticosteroids given with **NSAIDs**; increased risk of gastro-intestinal bleeding and ulceration when corticosteroids given with **aspirin**, also corticosteroids reduce plasma concentration of salicylate

Angiotensin-II Receptor Antagonists: corticosteroids antagonise hypotensive effect of **angiotensin-II receptor antagonists**

Antacids: absorption of deflazacort reduced by **antacids**

- **Antibacterials:** plasma concentration of methylprednisolone possibly increased by **clarithromycin**; metabolism of corticosteroids possibly inhibited by **erythromycin**; metabolism of methylprednisolone inhibited by **erythromycin**; corticosteroids possibly reduce plasma concentration of **isoniazid**; metabolism of corticosteroids accelerated by **rifamycins** (reduced effect)

- **Anticoagulants:** corticosteroids may enhance or reduce anticoagulant effect of **coumarins** (high-dose corticosteroids enhance anticoagulant effect); corticosteroids may enhance or reduce anticoagulant effect of **phenindione**

Antidiabetics: corticosteroids antagonise hypoglycaemic effect of **antidiabetics**

- **Antiepileptics:** metabolism of corticosteroids accelerated by **carbamazepine**, **phenobarbital** and **phenytoin** (reduced effect)

- **Antifungals:** increased risk of hypokalaemia when corticosteroids given with **amphotericin**—avoid concomitant use unless corticosteroids needed to control reactions; metabolism of corticosteroids and methylprednisolone possibly inhibited by **itraconazole**; plasma concentration of **inhaled** and **oral** (and possibly also **intranasal** and **rectal**) budesonide increased by **itraconazole**; plasma concentration of **inhaled** fluticasone increased by **itraconazole**; dexamethasone possibly reduces plasma concentration of **caspofungin**—consider increasing dose of caspofungin

- **Antivirals:** dexamethasone possibly reduces plasma concentration of **indinavir**, **lopinavir**, **saquinavir** and **telaprevir**; avoidance of dexamethasone (except when given as a single dose) advised by manufacturer of **rilpivirine**; plasma concentration of **inhaled** and **intranasal** fluticasone increased by **ritonavir**—increased risk of adrenal suppression; plasma con-

Corticosteroids• **Antivirals** (*continued*)

centration of budesonide (including **inhaled**, **intranasal**, and **rectal** budesonide) possibly increased by **ritonavir**—increased risk of adrenal suppression; plasma concentration of corticosteroids possibly increased by **ritonavir**—increased risk of adrenal suppression; plasma concentration of **inhaled** and **intranasal** budesonide and fluticasone possibly increased by **telaprevir**

Aprepitant: metabolism of dexamethasone and methylprednisolone inhibited by **aprepitant** (reduce dose of dexamethasone and methylprednisolone)

Beta-blockers: corticosteroids antagonise hypotensive effect of **beta-blockers**

Calcium Salts: corticosteroids reduce absorption of **calcium salts**

Calcium-channel Blockers: corticosteroids antagonise hypotensive effect of **calcium-channel blockers**; plasma concentration of methylprednisolone increased by **diltiazem**

Cardiac Glycosides: increased risk of hypokalaemia when corticosteroids given with **cardiac glycosides**

- **Ciclosporin:** high-dose methylprednisolone increases plasma concentration of **ciclosporin** (risk of convulsions); plasma concentration of prednisolone increased by **ciclosporin**

Clonidine: corticosteroids antagonise hypotensive effect of **clonidine**

Cytotoxics: possible increased risk of hepatotoxicity when dexamethasone given with **high-dose methotrexate**; dexamethasone possibly decreases plasma concentration of **axitinib** (increase dose of axitinib—consult axitinib product literature)

Diazoxide: corticosteroids antagonise hypotensive effect of **diazoxide**

Diuretics: corticosteroids antagonise diuretic effect of **diuretics**; increased risk of hypokalaemia when corticosteroids given with **acetazolamide**, **loop diuretics** or **thiazides** and related diuretics

Histamine: avoidance of corticosteroids advised by manufacturer of **histamine**

Methyldopa: corticosteroids antagonise hypotensive effect of **methyldopa**

Mifamurtide: avoidance of corticosteroids advised by manufacturer of **mifamurtide**

Mifepristone: effect of corticosteroids (including **inhaled** corticosteroids) may be reduced for 3–4 days after **mifepristone**

Moxonidine: corticosteroids antagonise hypotensive effect of **moxonidine**

Muscle Relaxants: corticosteroids possibly antagonise effects of **pancuronium** and **vecuronium**

Nitrates: corticosteroids antagonise hypotensive effect of **nitrates**

Oestrogens: plasma concentration of corticosteroids increased by oral contraceptives containing **oestrogens**

Sodium Benzoate: corticosteroids possibly reduce effects of **sodium benzoate**

Sodium Phenylbutyrate: corticosteroids possibly reduce effects of **sodium phenylbutyrate**

Somatropin: corticosteroids may inhibit growth-promoting effect of **somatropin**

Sympathomimetics: metabolism of dexamethasone accelerated by **ephedrine**

Sympathomimetics, Beta₂: increased risk of hypokalaemia when corticosteroids given with high doses of **beta₂ sympathomimetics**—*see* Hypokalaemia, p. 136

Theophylline: increased risk of hypokalaemia when corticosteroids given with **theophylline**

Ticagrelor: dexamethasone possibly reduces plasma concentration of **ticagrelor**

Corticosteroids (*continued*)

- Vaccines: high doses of corticosteroids impair immune response to **vaccines**, avoid concomitant use with live vaccines (see p. 604)

Vasodilator Antihypertensives: corticosteroids antagonise hypotensive effect of **hydralazine**, **minoxidil** and **sodium nitroprusside**

Co-trimoxazole *see* Trimethoprim and Sulfamethoxazole

Coumarins

Note Change in patient's clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect anticoagulant control

- Alcohol: anticoagulant control with coumarins may be affected by major changes in consumption of **alcohol**

Allopurinol: anticoagulant effect of coumarins possibly enhanced by **allopurinol**

- Anabolic Steroids: anticoagulant effect of coumarins enhanced by **anabolic steroids**

- Analgesics: anticoagulant effect of coumarins possibly enhanced by **NSAIDs**; increased risk of haemorrhage when anticoagulants given with *intravenous* **diclofenac** (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with **ketorolac** (avoid concomitant use, including low-dose heparins); anticoagulant effect of coumarins enhanced by **tramadol**; increased risk of bleeding when coumarins given with **aspirin** (due to antiplatelet effect); anticoagulant effect of coumarins possibly enhanced by prolonged regular use of **paracetamol**

- Anti-arrhythmics: metabolism of coumarins inhibited by **amiodarone** (enhanced anticoagulant effect); anticoagulant effect of warfarin may be enhanced or reduced by **disopyramide**; anticoagulant effect of coumarins possibly enhanced by **dronedrone**; anticoagulant effect of coumarins enhanced by **propafenone**

- Antibacterials: experience in anticoagulant clinics suggests that INR possibly altered when coumarins are given with **neomycin** (given for local action on gut); anticoagulant effect of coumarins possibly enhanced by **azithromycin**, **aztreonam**, **cephalosporins**, **ciprofloxacin**, **levofloxacin**, **tetracyclines**, **tigecycline** and **trimethoprim**; anticoagulant effect of coumarins enhanced by **chloramphenicol**, **clarithromycin**, **erythromycin**, **metronidazole**, **nalidixic acid**, **norfloxacin**, **ofloxacin** and **sulfonamides**; an interaction between coumarins and broad-spectrum **penicillins** has not been demonstrated in studies, but common experience in anticoagulant clinics is that INR can be altered; metabolism of coumarins accelerated by **rifamycins** (reduced anticoagulant effect)

- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with **apixaban**, **edogatan** and **rivaroxaban** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

- Antidepressants: anticoagulant effect of warfarin possibly enhanced by **venlafaxine**; anticoagulant effect of warfarin may be enhanced or reduced by **trazodone**; anticoagulant effect of coumarins possibly enhanced by **SSRIs**; anticoagulant effect of coumarins reduced by **St John's wort** (avoid concomitant use); anticoagulant effect of warfarin enhanced by **mirtazapine**; anticoagulant effect of coumarins may be enhanced or reduced by **tricyclics**

- Antidiabetics: anticoagulant effect of warfarin possibly enhanced by **exenatide**; coumarins possibly

Coumarins**Antidiabetics** (*continued*)

enhance hypoglycaemic effect of **sulfonylureas**, also possible changes to anticoagulant effect

- Antiepileptics: metabolism of coumarins accelerated by **carbamazepine** and **phenobarbital** (reduced anticoagulant effect); plasma concentration of warfarin reduced by **eslicarbazepine**; metabolism of coumarins accelerated by **phenytoin** (possibility of reduced anticoagulant effect, but enhancement also reported); anticoagulant effect of coumarins possibly enhanced by **valproate**

- Antifungals: anticoagulant effect of coumarins enhanced by **miconazole** (miconazole oral gel and possibly vaginal and topical formulations absorbed); anticoagulant effect of coumarins enhanced by **fluconazole**, **itraconazole** and **voriconazole**; anticoagulant effect of coumarins reduced by **griseofulvin**

Antimalarials: isolated reports that anticoagulant effect of warfarin may be enhanced by **proguanil**; plasma concentration of both drugs increased when warfarin given with **quinine**

- Antivirals: anticoagulant effect of warfarin may be enhanced or reduced by **atazanavir**, **nevirapine** and **ritonavir**; plasma concentration of coumarins possibly affected by **efavirenz**; anticoagulant effect of coumarins may be enhanced or reduced by **fosamprenavir**; anticoagulant effect of coumarins possibly enhanced by **ritonavir**; anticoagulant effect of warfarin possibly enhanced by **saquinavir**; plasma concentration of warfarin possibly affected by **telaprevir**

Anxiolytics and Hypnotics: anticoagulant effect of coumarins may transiently be enhanced by **chlordiazepoxide**

Apixaban: anticoagulant effect of warfarin possibly reduced by **apixaban**

- Azathioprine: anticoagulant effect of coumarins possibly reduced by **azathioprine**

Bosentan: monitoring anticoagulant effect of coumarins recommended by manufacturer of **bosentan**

- Clopidogrel: anticoagulant effect of coumarins enhanced due to antiplatelet action of **clopidogrel**; avoidance of warfarin advised by manufacturer of **clopidogrel**

- Corticosteroids: anticoagulant effect of coumarins may be enhanced or reduced by **corticosteroids** (high-dose corticosteroids enhance anticoagulant effect)

- Cranberry Juice: anticoagulant effect of coumarins possibly enhanced by **cranberry juice**—avoid concomitant use

- Cytotoxics: anticoagulant effect of coumarins possibly enhanced by **etoposide**, **ifosfamide** and **sorafenib**; anticoagulant effect of coumarins enhanced by **fluorouracil**; anticoagulant effect of warfarin possibly enhanced by **gefitinib**, **gemcitabine** and **vemurafenib**; anticoagulant effect of coumarins possibly reduced by **mercaptopurine** and **mitotane**; increased risk of bleeding when coumarins given with **erlotinib**; replacement of warfarin with a heparin advised by manufacturer of **imatinib** (possibility of enhanced warfarin effect); increased risk of bleeding when warfarin given with **regorafenib**

- Dipyridamole: anticoagulant effect of coumarins enhanced due to antiplatelet action of **dipyridamole**

- Disulfiram: anticoagulant effect of coumarins enhanced by **disulfiram**

- Dopaminergics: anticoagulant effect of warfarin enhanced by **entacapone**

- Enteral Foods: anticoagulant effect of coumarins antagonised by vitamin K (present in some **enteral feeds**)

- Glucosamine: anticoagulant effect of warfarin enhanced by **glucosamine** (avoid concomitant use)

Coumarins (*continued*)

- Hormone Antagonists: anticoagulant effect of coumarins possibly enhanced by **bicalutamide** and **•toremifene**; metabolism of coumarins inhibited by **•danazol** (enhanced anticoagulant effect); plasma concentration of coumarins possibly reduced by **•enzalutamide**; anticoagulant effect of coumarins enhanced by **•flutamide** and **•tamoxifen**
- Iloprost: anticoagulant effect of coumarins possibly enhanced by **•iloprost**
- Lactulose: anticoagulant effect of coumarins possibly enhanced by **•lactulose**
- Leflunomide: anticoagulant effect of warfarin possibly enhanced by **•leflunomide**
- Leukotriene Receptor Antagonists: anticoagulant effect of warfarin enhanced by **•zafirlukast**
- Levamisole: anticoagulant effect of warfarin possibly enhanced by **•levamisole**
- Levocarnitine: anticoagulant effect of coumarins possibly enhanced by **•levocarnitine**
- Lipid-regulating Drugs: anticoagulant effect of coumarins may be enhanced or reduced by **•colestyramine**; anticoagulant effect of warfarin may be transiently reduced by **•atorvastatin**; anticoagulant effect of coumarins enhanced by **•fibrates**, **•fluvastatin** and **•simvastatin**; anticoagulant effect of coumarins possibly enhanced by **•ezetimibe** and **•rosuvastatin**; anticoagulant effect of warfarin possibly enhanced by **•lomitapide**
- Memantine: anticoagulant effect of warfarin possibly enhanced by **•memantine**
- Oestrogens: anticoagulant effect of coumarins may be enhanced or reduced by **•oestrogens**
- Orlistat: monitoring anticoagulant effect of coumarins recommended by manufacturer of **•orlistat**
- Prasugrel: possible increased risk of bleeding when coumarins given with **•prasugrel**
- Progestogens: anticoagulant effect of coumarins may be enhanced or reduced by **•progestogens**
- Raloxifene: anticoagulant effect of coumarins antagonised by **•raloxifene**
- Retinoids: anticoagulant effect of coumarins possibly reduced by **•acitretin**
- Sulfapyrazone: anticoagulant effect of coumarins enhanced by **•sulfapyrazone**
- Sympathomimetics: anticoagulant effect of coumarins possibly enhanced by **•methylphenidate**
- Testolactone: anticoagulant effect of coumarins enhanced by **•testolactone**
- Testosterone: anticoagulant effect of coumarins enhanced by **•testosterone**
- Thyroid Hormones: anticoagulant effect of coumarins enhanced by **•thyroid hormones**
- Ubidecarenone: anticoagulant effect of warfarin may be enhanced or reduced by **•ubidecarenone**
- Ulcer-healing Drugs: metabolism of coumarins inhibited by **•cimetidine** (enhanced anticoagulant effect); anticoagulant effect of coumarins possibly enhanced by **•esomeprazole** and **•omeprazole**; anticoagulant effect of coumarins might be enhanced by **•pantoprazole**; absorption of coumarins possibly reduced by **•sucralfate** (reduced anticoagulant effect)
- Vaccines: anticoagulant effect of warfarin possibly enhanced by **•influenza vaccine**
- Vitamins: anticoagulant effect of coumarins possibly enhanced by **•vitamin E**; anticoagulant effect of coumarins antagonised by **•vitamin K**

Cranberry Juice

- Anticoagulants: cranberry juice possibly enhances anticoagulant effect of **•coumarins**—avoid concomitant use

Crizotinib

- Analgesics: manufacturer of crizotinib advises caution with **•alfentanil** and **•fentanyl**
- Antibacterials: plasma concentration of crizotinib possibly increased by **•clarithromycin** and **•telithromy-**

Crizotinib**Antibacterials** (*continued*)

- **cin**—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib possibly reduced by **•rifabutin**—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib reduced by **•rifampicin**—manufacturer of crizotinib advises avoid concomitant use
 - Antidepressants: plasma concentration of crizotinib possibly reduced by **•St John's wort**—manufacturer of crizotinib advises avoid concomitant use
 - Antiepileptics: plasma concentration of crizotinib possibly reduced by **•carbamazepine**, **•phenobarbital** and **•phenytoin**—manufacturer of crizotinib advises avoid concomitant use
 - Antifungals: plasma concentration of crizotinib possibly increased by **•itraconazole** and **•voriconazole**—manufacturer of crizotinib advises avoid concomitant use
 - Antimalarials: possible increased risk of bradycardia when crizotinib given with **•mefloquine**
 - Antipsychotics: avoid concomitant use of cytotoxics with **•clozapine** (increased risk of agranulocytosis); manufacturer of crizotinib advises caution with **•pimozide**
 - Antivirals: plasma concentration of crizotinib possibly increased by **•atazanavir**, **•indinavir**, **•ritonavir** and **•saquinavir**—manufacturer of crizotinib advises avoid concomitant use
 - Anxiolytics and Hypnotics: crizotinib increases plasma concentration of **•midazolam**
 - Beta-blockers: possible increased risk of bradycardia when crizotinib given with **•beta-blockers**
 - Calcium-channel Blockers: possible increased risk of bradycardia when crizotinib given with **•diltiazem** or **•verapamil**
 - Cardiac Glycosides: possible increased risk of bradycardia when crizotinib given with **•digoxin**
 - Ciclosporin: manufacturer of crizotinib advises caution with **•ciclosporin**
 - Clonidine: possible increased risk of bradycardia when crizotinib given with **•clonidine**
 - Ergot Alkaloids: manufacturer of crizotinib advises caution with **•ergot alkaloids**
 - Grapefruit Juice: plasma concentration of crizotinib possibly increased by **•grapefruit juice**—manufacturer of crizotinib advises avoid concomitant use
 - Oestrogens: manufacturer of crizotinib advises contraceptive effect of **•oestrogens** possibly reduced
 - Parasympathomimetics: possible increased risk of bradycardia when crizotinib given with **•pilocarpine**
 - Progestogens: manufacturer of crizotinib advises contraceptive effect of **•progestogens** possibly reduced
 - Sirolimus: manufacturer of crizotinib advises caution with **•sirolimus**
 - Tacrolimus: manufacturer of crizotinib advises caution with **•tacrolimus**
- Cyclizine** see Antihistamines
- Cyclopenthiiazide** see Diuretics
- Cyclopentolate** see Antimuscarinics
- Cyclophosphamide**
- Antifungals: side-effects of cyclophosphamide possibly increased by **•fluconazole** and **•itraconazole**
 - Antipsychotics: avoid concomitant use of cytotoxics with **•clozapine** (increased risk of agranulocytosis)
 - Cardiac Glycosides: cyclophosphamide possibly reduces absorption of **•digoxin tablets**
 - Cytotoxics: increased toxicity when high-dose cyclophosphamide given with **•pentostatin**—avoid concomitant use
 - Muscle Relaxants: cyclophosphamide enhances effects of **•suxamethonium**
- Cycloserine**
- Alcohol: increased risk of convulsions when cycloserine given with **•alcohol**

Cycloserine (continued)

Antibacterials: increased risk of CNS toxicity when cycloserine given with **isoniazid**

Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Cyproheptadine see Antihistamines**Cytarabine**

Antifungals: cytarabine possibly reduces plasma concentration of **flucytosine**

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Cardiac Glycosides: cytarabine possibly reduces absorption of **digoxin tablets**

Cytotoxics: intracellular concentration of cytarabine increased by **fludarabine**

Cytotoxics see individual drugs**Dabigatran**

- Analgesics: possible increased risk of bleeding when dabigatran given with **NSAIDs**; increased risk of haemorrhage when anticoagulants given with **intravenous diclofenac** (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with **ketorolac** (avoid concomitant use, including low-dose heparins)

- Anti-arrhythmics: plasma concentration of dabigatran increased by **amiodarone** (see Dose under Dabigatran, BNF section 2.8.2); plasma concentration of dabigatran increased by **dronedrone**—avoid concomitant use

- Antibacterials: possible increased risk of bleeding when dabigatran given with **clarithromycin**; plasma concentration of dabigatran reduced by **rifampicin**—manufacturer of dabigatran advises avoid concomitant use

- Anticoagulants: increased risk of haemorrhage when dabigatran given with other **anticoagulants** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when other anticoagulants given with **apixaban** and **rivaroxaban** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

- Antidepressants: possible increased risk of bleeding when dabigatran given with **SSRI-related antidepressants** or **SSRIs**; plasma concentration of dabigatran possibly reduced by **St John's wort**—manufacturer of dabigatran advises avoid concomitant use

Antiepileptics: plasma concentration of dabigatran possibly reduced by **carbamazepine** and **phenytoin**—manufacturer of dabigatran advises avoid concomitant use

Antifungals: manufacturer of dabigatran advises avoid concomitant use with **itraconazole**

Antivirals: plasma concentration of dabigatran possibly increased by **rilpivirine** and **telaprevir**

- Calcium-channel Blockers: plasma concentration of dabigatran possibly increased by **verapamil** (see Dose under Dabigatran, BNF section 2.8.2)

- Ciclosporin: plasma concentration of dabigatran possibly increased by **ciclosporin**—manufacturer of dabigatran advises avoid concomitant use

- Sulfinpyrazone: possible increased risk of bleeding when dabigatran given with **sulfinpyrazone**

- Tacrolimus: plasma concentration of dabigatran possibly increased by **tacrolimus**—manufacturer of dabigatran advises avoid concomitant use

- Ticagrelor: plasma concentration of dabigatran increased by **ticagrelor**

Ulipristal: manufacturer of ulipristal advises give dabigatran at least 1.5 hours before or after **ulipristal**

Dabrafenib

Antibacterials: manufacturer of dabrafenib advises avoid concomitant use with **rifampicin**

Dabrafenib (continued)

Antidepressants: manufacturer of dabrafenib advises avoid concomitant use with **St John's wort**

Antiepileptics: manufacturer of dabrafenib advises avoid concomitant use with **carbamazepine**, **phenobarbital** and **phenytoin**

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Oestrogens: manufacturer of dabrafenib advises contraceptive effect of hormonal contraceptives containing **oestrogens** possibly reduced (alternative contraceptive recommended)
- Progestogens: manufacturer of dabrafenib advises contraceptive effect of hormonal contraceptives containing **progestogens** possibly reduced (alternative contraceptive recommended)
- Ulcer-healing Drugs: manufacturer of dabrafenib advises avoid concomitant use with **proton pump inhibitors** (plasma concentration of dabrafenib possibly reduced)

Dacarbazine

- Aldesleukin: avoidance of dacarbazine advised by manufacturer of **aldesleukin**

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Dairy Products

Antibacterials: dairy products reduce absorption of **ciprofloxacin** and **norfloxacin**; dairy products reduce absorption of **tetracyclines** (except doxycycline and minocycline)

Cytotoxics: dairy products possibly reduce plasma concentration of **mercaptopurine**—manufacturer of mercaptopurine advises give at least 1 hour before or 2 hours after dairy products

Eltrombopag: dairy products possibly reduce absorption of **eltrombopag** (give at least 4 hours apart)

Dalteparin see Heparins**Danazol**

- Anticoagulants: danazol inhibits metabolism of **coumarins** (enhanced anticoagulant effect)
- Antiepileptics: danazol inhibits metabolism of **carbamazepine** (increased risk of toxicity)
- Ciclosporin: danazol inhibits metabolism of **ciclosporin** (increased plasma concentration)
- Lipid-regulating Drugs: possible increased risk of myopathy when danazol given with **simvastatin**—avoid concomitant use
- Tacrolimus: danazol possibly increases plasma concentration of **tacrolimus**

Dantrolene see Muscle Relaxants**Dapagliflozin** see Antidiabetics**Dapoxetine**

- Alcohol: increased sedative effect when dapoxetine given with **alcohol**
- Analgesics: possible increased risk of serotonergic effects when dapoxetine given with **tramadol** (manufacturer of dapoxetine advises tramadol should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tramadol)
- Antibacterials: manufacturer of dapoxetine advises dose reduction when dapoxetine given with **clarithromycin** and **erythromycin** (see Dose under Dapoxetine, BNF section 7.4.6); manufacturer of dapoxetine advises avoid concomitant use with **telithromycin** (increased risk of toxicity)
- Antidepressants: possible increased risk of serotonergic effects when dapoxetine given with **SSRIs**, **St John's wort**, **duloxetine**, **tricyclics** and **venlafaxine** (manufacturer of dapoxetine advises SSRIs, St John's wort, duloxetine, tricyclics and venlafaxine should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping SSRIs, St John's wort, duloxetine, tricyclics and venlafaxine); increased risk of serotonergic effects when dapoxetine given with

Dapoxetine

- Antidepressants (*continued*)
 - **MAOIs** (MAOIs should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping MAOIs)
- Antifungals: manufacturer of dapoxetine advises dose reduction when dapoxetine given with **fluconazole** (see Dose under Dapoxetine, BNf section 7.4.6); manufacturer of dapoxetine advises avoid concomitant use with **itraconazole** (increased risk of toxicity)
- Antivirals: manufacturer of dapoxetine advises avoid concomitant use with **atazanavir**, **ritonavir** and **saquinavir** (increased risk of toxicity); manufacturer of dapoxetine advises dose reduction when dapoxetine given with **fosamprenavir** (see Dose under Dapoxetine, BNf section 7.4.6)
- Aprepitant: manufacturer of dapoxetine advises dose reduction when dapoxetine given with **aprepitant** (see Dose under Dapoxetine, BNf section 7.4.6)
- Calcium-channel Blockers: manufacturer of dapoxetine advises dose reduction when dapoxetine given with **diltiazem** and **verapamil** (see Dose under Dapoxetine, BNf section 7.4.6)
- 5HT₁-receptor Agonists: possible increased risk of serotonergic effects when dapoxetine given with **5HT₁ agonists** (manufacturer of dapoxetine advises 5HT₁ agonists should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping 5HT₁ agonists)
- Lithium: possible increased risk of serotonergic effects when dapoxetine given with **lithium** (manufacturer of dapoxetine advises lithium should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping lithium)
- Sildenafil: manufacturer of dapoxetine advises avoid concomitant use with **sildenafil**
- Tadalafil: manufacturer of dapoxetine advises avoid concomitant use with **tadalafil**
- Vardenafil: manufacturer of dapoxetine advises avoid concomitant use with **vardenafil**

Dapsone

- Antibacterials: plasma concentration of dapsone reduced by **rifamycins**; plasma concentration of both drugs may increase when dapsone given with **trimethoprim**
- Antivirals: increased risk of ventricular arrhythmias when dapsone given with **saquinavir**—avoid concomitant use
- Probenecid: excretion of dapsone reduced by **probenecid** (increased risk of side-effects)
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Daptomycin

- Ciclosporin: increased risk of myopathy when daptomycin given with **ciclosporin** (preferably avoid concomitant use)
- Lipid-regulating Drugs: increased risk of myopathy when daptomycin given with **fibrates** or **statins** (preferably avoid concomitant use)
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Darifenacin see Antimuscarinics

Darunavir

- Anti-arrhythmics: darunavir possibly increases plasma concentration of **lidocaine**—avoid concomitant use
- Antibacterials: darunavir increases plasma concentration of **rifabutin** (reduce dose of rifabutin); plasma concentration of darunavir significantly reduced by **rifampicin**—avoid concomitant use
- Anticoagulants: avoidance of darunavir advised by manufacturer of **apixaban** and **rivaroxaban**
- Antidepressants: darunavir possibly increases plasma concentration of **paroxetine** and **sertraline**; plasma concentration of darunavir reduced by **St John's wort**—avoid concomitant use

Darunavir (*continued*)

- Antiepileptics: plasma concentration of darunavir possibly reduced by **carbamazepine**, **phenobarbital** and **phenytoin**
- Antimalarials: darunavir increases plasma concentration of **lumefantrine**; darunavir possibly increases plasma concentration of **quinine** (increased risk of toxicity)
- Antipsychotics: darunavir possibly increases plasma concentration of **aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); darunavir possibly increases plasma concentration of **quetiapine**—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: avoid concomitant use of darunavir with **boceprevir** or **telaprevir**; manufacturer of darunavir advises take **didanosine** 1 hour before or 2 hours after darunavir; plasma concentration of darunavir reduced by **efavirenz** (adjust dose—consult product literature); plasma concentration of both drugs increased when darunavir given with **indinavir**; plasma concentration of darunavir reduced by **lopinavir**, also plasma concentration of lopinavir increased (avoid concomitant use); darunavir increases plasma concentration of **maraviroc** (consider reducing dose of maraviroc); increased risk of rash when darunavir given with **raltegravir**; plasma concentration of darunavir reduced by **saquinavir**
- Cytotoxics: darunavir possibly increases the plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; darunavir possibly increases plasma concentration of **everolimus**—manufacturer of everolimus advises avoid concomitant use
- Ergot Alkaloids: increased risk of ergotism when darunavir given with **ergot alkaloids**—manufacturer of darunavir advises avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when darunavir given with **atorvastatin**; darunavir possibly increases plasma concentration of **pravastatin**; possible increased risk of myopathy when darunavir given with **rosuvastatin**—manufacturer of rosuvastatin advises avoid concomitant use; avoidance of darunavir advised by manufacturer of **lomitapide** (plasma concentration of lomitapide possibly increased)
- Orlistat: absorption of darunavir possibly reduced by **orlistat**
- Ranolazine: darunavir possibly increases plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use

Dasatinib

- Antibacterials: metabolism of dasatinib accelerated by **rifampicin** (reduced plasma concentration—avoid concomitant use)
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Antivirals: avoidance of dasatinib advised by manufacturer of **boceprevir**
- Lipid-regulating Drugs: dasatinib possibly increases plasma concentration of **simvastatin**
- Ulcer-healing Drugs: plasma concentration of dasatinib possibly reduced by **famotidine**

Decitabine

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Deferasirox

- Antacids: absorption of deferasirox possibly reduced by **antacids** containing aluminium (manufacturer of deferasirox advises avoid concomitant use)
- Antibacterials: plasma concentration of deferasirox reduced by **rifampicin**
- Antidiabetics: deferasirox increases plasma concentration of **repaglinide**
- Antipsychotics: manufacturer of deferasirox advises avoid concomitant use with **clozapine**

Deferasirox (*continued*)

- Anxiolytics and Hypnotics: deferasirox possibly reduces plasma concentration of **midazolam**
- Muscle Relaxants: manufacturer of deferasirox advises avoid concomitant use with **tizanidine**
- Theophylline: deferasirox increases plasma concentration of **theophylline** (consider reducing dose of theophylline)

Deferiprone

- Antacids: absorption of deferiprone possibly reduced by **antacids** containing aluminium (manufacturer of deferiprone advises avoid concomitant use)

Deflazacort *see* Corticosteroids**Demeclocycline** *see* Tetracyclines**Desferrioxamine**

- Antipsychotics: avoidance of desferrioxamine advised by manufacturer of **levomepromazine**; manufacturer of desferrioxamine advises avoid concomitant use with **prochlorperazine**

Desflurane *see* Anaesthetics, General**Desloratadine** *see* Antihistamines**Desmopressin**

- Analgesics: effects of desmopressin enhanced by **indometacin**
- Loperamide: plasma concentration of *oral* desmopressin increased by **loperamide**

Desogestrel *see* Progestogens**Dexamethasone** *see* Corticosteroids**Dexamfetamine** *see* Sympathomimetics**Dexibuprofen** *see* NSAIDs**Dexketoprofen** *see* NSAIDs**Dextromethorphan** *see* Opioid Analgesics**Dextropropoxyphene** *see* Opioid Analgesics**Diamorphine** *see* Opioid Analgesics**Diazepam** *see* Anxiolytics and Hypnotics**Diazoxide**

- ACE Inhibitors: enhanced hypotensive effect when diazoxide given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when diazoxide given with **adrenergic neurone blockers**
- Alcohol: enhanced hypotensive effect when diazoxide given with **alcohol**
- Aldesleukin: enhanced hypotensive effect when diazoxide given with **aldesleukin**
- Alpha-blockers: enhanced hypotensive effect when diazoxide given with **alpha-blockers**
- Anaesthetics, General: enhanced hypotensive effect when diazoxide given with **general anaesthetics**
- Analgesics: hypotensive effect of diazoxide antagonised by **NSAIDs**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when diazoxide given with **angiotensin-II receptor antagonists**
- Antidepressants: enhanced hypotensive effect when diazoxide given with **MAOIs** or **tricyclic-related antidepressants**
- Antidiabetics: diazoxide antagonises hypoglycaemic effect of **antidiabetics**
- Antiepileptics: diazoxide reduces plasma concentration of **phenytoin**, also effect of diazoxide may be reduced
- Antipsychotics: enhanced hypotensive effect when diazoxide given with **phenothiazines**
- Anxiolytics and Hypnotics: enhanced hypotensive effect when diazoxide given with **anxiolytics and hypnotics**
- Beta-blockers: enhanced hypotensive effect when diazoxide given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when diazoxide given with **calcium-channel blockers**
- Clonidine: enhanced hypotensive effect when diazoxide given with **clonidine**

Diazoxide (*continued*)

- Corticosteroids: hypotensive effect of diazoxide antagonised by **corticosteroids**
- Diuretics: enhanced hypotensive and hyperglycaemic effects when diazoxide given with **diuretics**
- Dopaminergics: enhanced hypotensive effect when diazoxide given with **levodopa**
- Methyldopa: enhanced hypotensive effect when diazoxide given with **methyldopa**
- Moxisylyte: enhanced hypotensive effect when diazoxide given with **moxisylyte**
- Moxonidine: enhanced hypotensive effect when diazoxide given with **moxonidine**
- Muscle Relaxants: enhanced hypotensive effect when diazoxide given with **baclofen** or **tizanidine**
- Nitrates: enhanced hypotensive effect when diazoxide given with **nitrates**
- Prostaglandins: enhanced hypotensive effect when diazoxide given with **alprostadi**
- Vasodilator Antihypertensives: enhanced hypotensive effect when diazoxide given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Diclofenac *see* NSAIDs**Dicycloverine** *see* Antimuscarinics**Didanosine**

- Note** Antacids in tablet formulation might affect absorption of other drugs—give at least 2 hours apart
- Allopurinol: plasma concentration of didanosine increased by **allopurinol** (risk of toxicity)—avoid concomitant use
 - Analgesics: plasma concentration of didanosine possibly reduced by **methadone**
 - Antibacterials: manufacturer of norfloxacin advises give didanosine at least 2 hours before or after **norfloxacin**
 - Antivirals: didanosine *tablets* reduce absorption of **atazanavir** (give at least 2 hours before or 1 hour after didanosine *tablets*); manufacturer of darunavir advises take didanosine 1 hour before or 2 hours after **darunavir**; plasma concentration of didanosine possibly increased by **ganciclovir**; didanosine *tablets* reduce absorption of **indinavir** (give at least 1 hour apart); increased risk of side-effects when didanosine given with **ribavirin**—avoid concomitant use; manufacturer of rilpivirine advises give didanosine 2 hours before or 4 hours after **rilpivirine**; manufacturer of ritonavir advises didanosine and **ritonavir** should be taken 2.5 hours apart; increased risk of side-effects when didanosine given with **stavudine**; plasma concentration of didanosine increased by **tenofovir** (increased risk of toxicity)—avoid concomitant use; plasma concentration of didanosine reduced by **tipranavir**—manufacturer of tipranavir advises tipranavir and didanosine *capsules* should be taken at least 2 hours apart
 - Cytotoxics: increased risk of toxicity when didanosine given with **hydroxycarbamide**—avoid concomitant use
 - Orlistat: absorption of didanosine possibly reduced by **orlistat**

Dienogest *see* Progestogens**Digoxin** *see* Cardiac Glycosides**Dihydrocodeine** *see* Opioid Analgesics**Diltiazem** *see* Calcium-channel Blockers**Dimethyl sulfoxide**

- Analgesics: avoid concomitant use of dimethyl sulfoxide with **sulindac**

Dinoprostone *see* Prostaglandins**Diphenoxylate** *see* Opioid Analgesics**Dipipanone** *see* Opioid Analgesics**Dipyridamole**

- Antacids: absorption of dipyridamole possibly reduced by **antacids**
- Anti-arrhythmics: dipyridamole enhances and extends effect of **adenosine** (important risk of

Dipyridamole

- Anti-arrhythmics (*continued*)
toxicity)—reduce dose of adenosine, see Dose under Adenosine, p. 82
- Anticoagulants: antiplatelet action of dipyridamole enhances anticoagulant effect of ●**coumarins** and ●**phenindione**; dipyridamole enhances anticoagulant effect of ●**heparins**

Clopidogrel: increased risk of bleeding when dipyridamole given with ●**clopidogrel**

Cytotoxics: dipyridamole possibly reduces effects of ●**fludarabine**

Disopyramide

Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with ●**bupivacaine**, ●**levobupivacaine**, ●**prilocaine** or ●**ropivacaine**

- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other ●**anti-arrhythmics**; increased risk of ventricular arrhythmias when disopyramide given with ●**amiodarone** or ●**dronedarone**—avoid concomitant use
- Antibacterials: plasma concentration of disopyramide possibly increased by ●**azithromycin** (increased risk of toxicity); plasma concentration of disopyramide possibly increased by ●**clarithromycin** (increased risk of ventricular arrhythmias); plasma concentration of disopyramide increased by ●**erythromycin** (increased risk of toxicity); increased risk of ventricular arrhythmias when disopyramide given with ●**moxifloxacin**—avoid concomitant use; metabolism of disopyramide accelerated by ●**rifamycins** (reduced plasma concentration); possible increased risk of ventricular arrhythmias when disopyramide given with ●**telithromycin**

Anticoagulants: disopyramide may enhance or reduce anticoagulant effect of ●**warfarin**

- Antidepressants: avoidance of disopyramide advised by manufacturer of ●**citalopram** and ●**escitalopram** (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when disopyramide given with ●**tricyclics**

Antidiabetics: disopyramide possibly enhances hypoglycaemic effect of ●**gliclazide**, ●**insulin** and ●**metformin**

Antiepileptics: metabolism of disopyramide accelerated by ●**phenobarbital** (reduced plasma concentration); plasma concentration of disopyramide reduced by ●**phenytoin**

- Antifungals: avoidance of disopyramide advised by manufacturer of ●**itraconazole**
- Antihistamines: increased risk of ventricular arrhythmias when disopyramide given with ●**mizolastine**—avoid concomitant use
- Antimalarials: avoidance of disopyramide advised by manufacturer of ●**piperaquine** with ●**artemisinin** (possible risk of ventricular arrhythmias); avoidance of disopyramide advised by manufacturer of ●**artemether** with ●**lumefantrine** (risk of ventricular arrhythmias)
- Antimuscarinics: increased risk of antimuscarinic side-effects when disopyramide given with ●**antimuscarinics**; increased risk of ventricular arrhythmias when disopyramide given with ●**tolterodine**
- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with ●**antipsychotics** that prolong the QT interval; increased risk of ventricular arrhythmias when disopyramide given with ●**amisulpride**, ●**droperidol**, ●**pimozide** or ●**zuclopentixol**—avoid concomitant use; possible increased risk of ventricular arrhythmias when disopyramide given with ●**haloperidol**—avoid concomitant use; increased risk of ventricular arrhythmias when disopyramide given with ●**phenothiazines** or ●**sulpiride**
- Antivirals: plasma concentration of disopyramide possibly increased by ●**ritonavir** (increased risk of toxicity); increased risk of ventricular arrhythmias when

Disopyramide

- Antivirals (*continued*)
disopyramide given with ●**saquinavir**—avoid concomitant use; avoidance of disopyramide advised by manufacturer of ●**telaprevir** (risk of ventricular arrhythmias)
- Atomoxetine: increased risk of ventricular arrhythmias when disopyramide given with ●**atomoxetine**
- Beta-blockers: increased myocardial depression when anti-arrhythmics given with ●**beta-blockers**; increased risk of ventricular arrhythmias when disopyramide given with ●**sotalol**—avoid concomitant use
- Calcium-channel Blockers: increased risk of myocardial depression and asystole when disopyramide given with ●**verapamil**
- Cytotoxics: possible increased risk of ventricular arrhythmias when disopyramide given with ●**bosutinib**; possible increased risk of ventricular arrhythmias when disopyramide given with ●**vandetanib**—avoid concomitant use; increased risk of ventricular arrhythmias when disopyramide given with ●**arsenic trioxide**
- Diuretics: increased cardiac toxicity with disopyramide if hypokalaemia occurs with ●**acetazolamide**, ●**loop diuretics** or ●**thiazides and related diuretics**
- Fingolimod: possible increased risk of bradycardia when disopyramide given with ●**fingolimod**
- Ivabradine: increased risk of ventricular arrhythmias when disopyramide given with ●**ivabradine**
- Nitrates: disopyramide reduces effects of sublingual tablets of ●**nitrates** (failure to dissolve under tongue owing to dry mouth)
- Pentamidine Isetionate: possible increased risk of ventricular arrhythmias when disopyramide given with ●**pentamidine isetionate**
- Ranolazine: avoidance of disopyramide advised by manufacturer of ●**ranolazine**
- Sildenafil: manufacturer of disopyramide advises avoid concomitant use with ●**sildenafil** (risk of ventricular arrhythmias)
- Tadalafil: manufacturer of disopyramide advises avoid concomitant use with ●**tadalafil** (risk of ventricular arrhythmias)
- Vardenafil: manufacturer of disopyramide advises avoid concomitant use with ●**vardenafil** (risk of ventricular arrhythmias)

Disulfiram

Alcohol: disulfiram reaction when disulfiram given with ●**alcohol** (see BNF section 4.10.1)

Antibacterials: psychotic reaction reported when disulfiram given with ●**metronidazole**; CNS effects of disulfiram possibly increased by ●**isoniazid**

- Anticoagulants: disulfiram enhances anticoagulant effect of ●**coumarins**
- Antidepressants: increased disulfiram reaction with alcohol reported with concomitant ●**amitriptyline**; disulfiram inhibits metabolism of ●**tricyclics** (increased plasma concentration)
- Antiepileptics: disulfiram inhibits metabolism of ●**phenytoin** (increased risk of toxicity)
- Anxiolytics and Hypnotics: disulfiram increases risk of ●**temazepam** toxicity; disulfiram inhibits metabolism of ●**benzodiazepines** (increased sedative effects)
- Paraldehyde: risk of toxicity when disulfiram given with ●**paraldehyde**
- Theophylline: disulfiram inhibits metabolism of ●**theophylline** (increased risk of toxicity)

Diuretics

Note Since systemic absorption may follow topical application of brinzolamide to the eye, the possibility of interactions should be borne in mind

Note Since systemic absorption may follow topical application of dorzolamide to the eye, the possibility of interactions should be borne in mind

Diuretics (*continued*)

- ACE Inhibitors: enhanced hypotensive effect when diuretics given with **ACE inhibitors**; increased risk of severe hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when diuretics given with **adrenergic neurone blockers**
- Alcohol: enhanced hypotensive effect when diuretics given with **alcohol**
- Aldesleukin: enhanced hypotensive effect when diuretics given with **aldesleukin**
- Aliskiren: plasma concentration of furosemide reduced by **aliskiren**; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **aliskiren**
- Allopurinol: increased risk of hypersensitivity when thiazides and related diuretics given with **allopurinol** especially in renal impairment
- Alpha-blockers: enhanced hypotensive effect when diuretics given with **alpha-blockers**, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Anaesthetics, General: enhanced hypotensive effect when diuretics given with **general anaesthetics**
- Analgesics: possible increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **NSAIDs**; diuretics increase risk of nephrotoxicity of **NSAIDs**, also antagonism of diuretic effect; Diuretic effect of potassium canrenoate possibly antagonised by **NSAIDs**; furosemide possibly increases the excretion of **acetaminophen**; effects of diuretics antagonised by **indometacin** and **ketorolac**; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **indometacin**; occasional reports of reduced renal function when tramterene given with **indometacin**—avoid concomitant use; diuretic effect of spironolactone antagonised by **aspirin**; possible increased risk of toxicity when loop diuretics given with high-dose **aspirin** (also possible reduced effect of loop diuretics); increased risk of toxicity when acetazolamide given with high-dose **aspirin**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when diuretics given with **angiotensin-II receptor antagonists**; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **angiotensin-II receptor antagonists**
- Anti-arrhythmics: plasma concentration of eplerenone increased by **amiodarone** (reduce dose of eplerenone); hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with **amiodarone**; hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with **disopyramide**; hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with **flecainide**; hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics antagonises action of **lidocaine**
- Antibacterials: plasma concentration of eplerenone increased by **clarithromycin** and **telithromycin**—avoid concomitant use; plasma concentration of eplerenone increased by **erythromycin** (reduce dose of eplerenone); plasma concentration of eplerenone reduced by **rifampicin**—avoid concomitant use; avoidance of diuretics advised by manufacturer of **lymecycline**; increased risk of toxicity when loop diuretics given with **aminoglycosides**, **polymyxins** or **vancomycin**; acetazolamide antagonises effects of **methenamine**; possible increased risk of hyperkalaemia when spironolactone given with **trimetho-**

Diuretics

- Antibacterials (*continued*)
 - prim**; increased risk of hyperkalaemia when eplerenone given with **trimethoprim**
- Antidepressants: possible increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with **reboxetine**; enhanced hypotensive effect when diuretics given with **MAOIs**; plasma concentration of eplerenone reduced by **St John's wort**—avoid concomitant use; increased risk of postural hypotension when diuretics given with **tricyclics**
- Antidiabetics: loop diuretics and thiazides and related diuretics antagonise hypoglycaemic effect of **antidiabetics**; diuretic effect of diuretics possibly enhanced by **canagliflozin**; avoidance of loop diuretics advised by manufacturer of **canagliflozin**; diuretic effect of loop diuretics and thiazides and related diuretics possibly enhanced by **dapagliflozin**
- Antiepileptics: plasma concentration of eplerenone reduced by **carbamazepine**, **phenobarbital** and **phenytoin**—avoid concomitant use; increased risk of hyponatraemia when diuretics given with **carbamazepine**; acetazolamide increases plasma concentration of **carbamazepine**; increased risk of osteomalacia when carbonic anhydrase inhibitors given with **phenobarbital** or **phenytoin**; effects of furosemide antagonised by **phenytoin**; acetazolamide possibly increases plasma concentration of **phenytoin**; hydrochlorothiazide possibly increases plasma concentration of **topiramate**; avoidance of carbonic anhydrase inhibitors in children advised by manufacturer of **zonisamide**
- Antifungals: increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with **amphotericin**; hydrochlorothiazide increases plasma concentration of **fluconazole**; plasma concentration of eplerenone increased by **fluconazole** (reduce dose of eplerenone); plasma concentration of eplerenone increased by **itraconazole**—avoid concomitant use
- Antipsychotics: hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with **amisulpride**; enhanced hypotensive effect when diuretics given with **phenothiazines**; hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with **pimozide** (avoid concomitant use)
- Antivirals: plasma concentration of eplerenone increased by **ritonavir**—avoid concomitant use; plasma concentration of eplerenone increased by **saquinavir** (reduce dose of eplerenone)
- Anxiolytics and Hypnotics: enhanced hypotensive effect when diuretics given with **anxiolytics** and **hypnotics**; administration of **parenteral** furosemide with **chlorthal** may displace thyroid hormone from binding sites
- Atomoxetine: hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with **atomoxetine**
- Beta-blockers: enhanced hypotensive effect when diuretics given with **beta-blockers**; hypokalaemia caused by loop diuretics or thiazides and related diuretics increases risk of ventricular arrhythmias with **sotalol**
- Calcium Salts: increased risk of hypercalcaemia when thiazides and related diuretics given with **calcium salts**
- Calcium-channel Blockers: enhanced hypotensive effect when diuretics given with **calcium-channel blockers**; plasma concentration of eplerenone increased by **diltiazem** and **verapamil** (reduce dose of eplerenone)
- Cardiac Glycosides: hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with **cardiac glyco-**

Diuretics

- Cardiac Glycosides (*continued*)
 - sides*; potassium canrenoate possibly increases plasma concentration of **digoxin**; spironolactone increases plasma concentration of **digoxin**
- Ciclosporin: increased risk of nephrotoxicity and possibly hypermagnesaemia when thiazides and related diuretics given with **ciclosporin**; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **ciclosporin**; acetazolamide possibly increases plasma concentration of **ciclosporin**
- Clonidine: enhanced hypotensive effect when diuretics given with **clonidine**
- Corticosteroids: diuretic effect of diuretics antagonised by **corticosteroids**; increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with **corticosteroids**
- Cytotoxics: alkaline urine due to acetazolamide increases excretion of **methotrexate**; hyperkalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases risk of ventricular arrhythmias with **arsenic trioxide**; avoidance of spironolactone advised by manufacturer of **mitotane** (antagonism of effect); increased risk of nephrotoxicity and ototoxicity when diuretics given with **platinum compounds**
- Diazoxide: enhanced hypotensive and hyperglycaemic effects when diuretics given with **diazoxide**
- Diuretics: increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with **acetazolamide**; profound diuresis possible when metolazone given with **furosemide**; increased risk of hypokalaemia when thiazides and related diuretics given with **loop diuretics**
- Dopaminergics: enhanced hypotensive effect when diuretics given with **levodopa**
- Hormone Antagonists: increased risk of hypercalcaemia when thiazides and related diuretics given with **toremifene**
- Lipid-regulating Drugs: absorption of thiazides and related diuretics reduced by **colestipol** and **colestyramine** (give at least 2 hours apart)
- Lithium: loop diuretics and thiazides and related diuretics reduce excretion of **lithium** (increased plasma concentration and risk of toxicity)—loop diuretics safer than thiazides; potassium-sparing diuretics and aldosterone antagonists reduce excretion of **lithium** (increased plasma concentration and risk of toxicity); acetazolamide increases the excretion of **lithium**
- Methyldopa: enhanced hypotensive effect when diuretics given with **methyldopa**
- Moxisylyte: enhanced hypotensive effect when diuretics given with **moxisylyte**
- Moxonidine: enhanced hypotensive effect when diuretics given with **moxonidine**
- Muscle Relaxants: enhanced hypotensive effect when diuretics given with **baclofen** or **tizanidine**
- Nitrates: enhanced hypotensive effect when diuretics given with **nitrates**
- Oestrogens: diuretic effect of diuretics antagonised by **oestrogens**
- Potassium Salts: increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **potassium salts**
- Progestogens: risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **drospirenone** (monitor serum potassium during first cycle)
- Prostaglandins: enhanced hypotensive effect when diuretics given with **alprostadil**
- Sympathomimetics, Beta₂: increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with high doses

Diuretics

Sympathomimetics, Beta₂ (*continued*)

of **beta₂ sympathomimetics**—see Hypokalaemia, p. 136

- Tacrolimus: increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **tacrolimus**
- Theophylline: increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with **theophylline**
- Vasodilator Antihypertensives: enhanced hypotensive effect when diuretics given with **hydralazine**, **minoxidil** or **sodium nitroprusside**
- Vitamins: increased risk of hypercalcaemia when thiazides and related diuretics given with **vitamin D**

Diuretics, Loop *see* Diuretics

Diuretics, Potassium-sparing and Aldosterone

Antagonists *see* Diuretics

Diuretics, Thiazide and related *see* Diuretics

Dobutamine *see* Sympathomimetics

Docetaxel

Antibacterials: *in vitro* studies suggest a possible interaction between docetaxel and **erythromycin** (consult docetaxel product literature)

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Antivirals: plasma concentration of docetaxel possibly increased by **ritonavir** (increased risk of toxicity)
- Ciclosporin: *in vitro* studies suggest a possible interaction between docetaxel and **ciclosporin** (consult docetaxel product literature)
- Cytotoxics: possible increased risk of neutropenia when docetaxel given with **lapatinib**; plasma concentration of docetaxel increased by **sorafenib**

Dolutegravir

Antacids: absorption of dolutegravir possibly reduced by **aluminium hydroxide** and **oral magnesium salts**—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after aluminium hydroxide and oral magnesium salts

- Antibacterials: plasma concentration of dolutegravir reduced by **rifampicin** (see Dose under Dolutegravir, p. 324)
- Antidepressants: manufacturer of dolutegravir advises avoid concomitant use with **St John's wort**
- Antiepileptics: manufacturer of dolutegravir advises avoid concomitant use with **carbamazepine**, **oxcarbazepine**, **phenobarbital** and **phenytoin**
- Antivirals: plasma concentration of dolutegravir reduced by **efavirenz** and **tipranavir** (see Dose under Dolutegravir, p. 324); plasma concentration of dolutegravir reduced by **etravirine** (see Cautions under Dolutegravir, p. 324); plasma concentration of dolutegravir reduced by **fosamprenavir**; plasma concentration of dolutegravir possibly reduced by **nevirapine** (see Dose under Dolutegravir, p. 324)
- Calcium Salts: absorption of dolutegravir possibly reduced by **calcium salts**—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after calcium salts

Domperidone

Analgesics: effects of domperidone on gastro-intestinal activity antagonised by **opioid analgesics**

- Antibacterials: plasma concentration of domperidone increased by **erythromycin**—possible increased risk of ventricular arrhythmias
- Antimalarials: avoidance of domperidone advised by manufacturer of **piperazine with arteminimol** (possible risk of ventricular arrhythmias)
- Antimuscarinics: effects of domperidone on gastro-intestinal activity antagonised by **antimuscarinics**
- Antivirals: plasma concentration of domperidone possibly increased by **telaprevir**—manufacturer of telaprevir advises avoid concomitant use

Domperidone (continued)

- Cytotoxics: avoidance of domperidone advised by manufacturer of **●bosutinib** (risk of ventricular arrhythmias)
- Dopaminergics: domperidone possibly antagonises hypoprolactinaemic effects of **bromocriptine** and **cabergoline**

Donepezil *see* Parasympathomimetics

Dopamine *see* Sympathomimetics

Dopaminergics *see* Amantadine, Apomorphine, Bromocriptine, Cabergoline, Entacapone, Levodopa, Pergolide, Pramipexole, Quinagolide, Rasagiline, Ropinirole, Rotigotine, Selegiline, and Tolcapone

Dopexamine *see* Sympathomimetics

Dorzolamide *see* Diuretics

Dosulepin *see* Antidepressants, Tricyclic

Doxapram

- Anaesthetics, General: increased risk of arrhythmias when doxapram given with **●volatile liquid general anaesthetics** (avoid doxapram for at least 10 minutes after volatile liquid general anaesthetics)

Antidepressants: effects of doxapram enhanced by **MAOIs**

Sympathomimetics: increased risk of hypertension

when doxapram given with **sympathomimetics**

Theophylline: increased CNS stimulation when doxapram given with **theophylline**

Doxazosin *see* Alpha-blockers

Doxepin *see* Antidepressants, Tricyclic

Doxorubicin

- Antipsychotics: avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)
- Antivirals: doxorubicin possibly inhibits effects of **stavudine**
- Calcium-channel Blockers: plasma concentration of doxorubicin possibly increased by **verapamil**
- Cardiac Glycosides: doxorubicin possibly reduces absorption of **digoxin tablets**
- Ciclosporin: increased risk of neurotoxicity when doxorubicin given with **●ciclosporin**
- Cytotoxics: plasma concentration of doxorubicin possibly increased by **sorafenib**

Doxycycline *see* Tetracyclines

Dronedrone

- Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with **bupivacaine**, **levobupivacaine**, **prilocaine** or **ropivacaine**
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other **●anti-arrhythmics**; increased risk of ventricular arrhythmias when dronedarone given with **●amiodarone** or **●disopyramide**—avoid concomitant use
- Antibacterials: manufacturer of dronedarone advises avoid concomitant use with **●clarithromycin** (risk of ventricular arrhythmias); plasma concentration of dronedarone increased by **●erythromycin** (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of dronedarone reduced by **●rifampicin**—avoid concomitant use; increased risk of ventricular arrhythmias when dronedarone given with **●telithromycin**—avoid concomitant use
- Anticoagulants: dronedarone possibly enhances anticoagulant effect of **●coumarins** and **●phenindione**; dronedarone increases plasma concentration of **●dabigatran**—avoid concomitant use; avoidance of dronedarone advised by manufacturer of **rivaroxaban**
- Antidepressants: avoidance of dronedarone advised by manufacturer of **●citalopram** and **●escitalopram** (risk of ventricular arrhythmias); plasma concentration of dronedarone possibly reduced by **●St John's wort**—avoid concomitant use; manufacturer of dronedarone advises avoid concomitant use with **●tricyclics** (risk of ventricular arrhythmias)

Dronedrone (continued)

- Antiepileptics: plasma concentration of dronedarone possibly reduced by **●carbamazepine**, **●phenobarbital** and **●phenytoin**—avoid concomitant use
 - Antifungals: manufacturer of dronedarone advises avoid concomitant use with **●itraconazole**, **●posaconazole** and **●voriconazole**
 - Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with **●antipsychotics** that prolong the QT interval; manufacturer of dronedarone advises avoid concomitant use with **●phenothiazines** (risk of ventricular arrhythmias)
 - Antivirals: manufacturer of dronedarone advises avoid concomitant use with **●ritonavir**; increased risk of ventricular arrhythmias when dronedarone given with **●saquinavir**—avoid concomitant use
 - Beta-blockers: increased myocardial depression when anti-arrhythmics given with **●beta-blockers**; dronedarone possibly increases plasma concentration of **metoprolol** and **propranolol**; increased risk of ventricular arrhythmias when dronedarone given with **●sotalol**—avoid concomitant use
 - Calcium-channel Blockers: plasma concentration of dronedarone increased by **●nifedipine**; increased risk of bradycardia and myocardial depression when dronedarone given with **●diltiazem** and **●verapamil**
 - Cardiac Glycosides: dronedarone increases plasma concentration of **●digoxin** (halve dose of digoxin)
 - Cytotoxics: dronedarone possibly increases the plasma concentration of **●bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
 - Fidaxomicin: avoidance of dronedarone advised by manufacturer of **fidaxomicin**
 - Fingolimod: possible increased risk of bradycardia when dronedarone given with **●fingolimod**
 - Grapefruit Juice: plasma concentration of dronedarone increased by **●grapefruit juice**—avoid concomitant use
 - Lipid-regulating Drugs: dronedarone possibly increases plasma concentration of **atorvastatin** and **rosuvastatin**; increased risk of myopathy when dronedarone given with **●simvastatin**; avoidance of dronedarone advised by manufacturer of **●lomitapide** (plasma concentration of lomitapide possibly increased)
 - Sirolimus: manufacturer of dronedarone advises caution with **sirolimus**
 - Tacrolimus: manufacturer of dronedarone advises caution with **tacrolimus**
- Droperidol** *see* Antipsychotics
- Drosiprenone** *see* Progestogens
- Duloxetine**
- Analgesics: possible increased serotonergic effects when SSRI-related antidepressants given with **fentanyl**; possible increased serotonergic effects when duloxetine given with **pethidine** or **tramadol**
 - Antibacterials: metabolism of duloxetine inhibited by **●ciprofloxacin**—avoid concomitant use
 - Anticoagulants: possible increased risk of bleeding when SSRI-related antidepressants given with **●dabigatran**
 - Antidepressants: metabolism of duloxetine inhibited by **●fluvoxamine**—avoid concomitant use; possible increased serotonergic effects when duloxetine given with SSRIs, **St John's wort**, **amitriptyline**, **clomipramine**, **●moclobemide** or **venlafaxine**; duloxetine should not be started until 2 weeks after stopping **●MAOIs**, also MAOIs should not be started until at least 5 days after stopping duloxetine; after stopping SSRI-related antidepressants do not start **●moclobemide** for at least 1 week

Duloxetine (*continued*)

- Antimalarials: avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperaquine with arteminol**

Atomoxetine: possible increased risk of convulsions when antidepressants given with **atomoxetine**

- Dapoxetine: possible increased risk of serotonergic effects when duloxetine given with **dapoxetine** (manufacturer of dapoxetine advises duloxetine should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping duloxetine)

5HT₁-receptor Agonists: possible increased serotonergic effects when duloxetine given with **5HT₁ agonists**

- Methylthioninium: risk of CNS toxicity when SSRI-related antidepressants given with **methylthioninium**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

Dutasteride

Calcium-channel Blockers: plasma concentration of dutasteride increased by **diltiazem** and **verapamil**

Dydrogesterone *see* Progestogens

Edrophonium *see* Parasympathomimetics

Efavirenz

Analgesics: efavirenz reduces plasma concentration of **methadone**

Antibacterials: efavirenz reduces plasma concentration of **clarithromycin**, also plasma concentration of active metabolite of clarithromycin increased; efavirenz reduces plasma concentration of **rifabutin**—increase dose of rifabutin; plasma concentration of efavirenz reduced by **rifampicin**—increase dose of efavirenz

- Anticoagulants: efavirenz possibly affects plasma concentration of **coumarins**

- Antidepressants: plasma concentration of efavirenz reduced by **St John's wort**—avoid concomitant use

Antiepileptics: plasma concentration of both drugs reduced when efavirenz given with **carbamazepine**

- Antifungals: efavirenz reduces plasma concentration of **itraconazole** and **posaconazole**; efavirenz reduces plasma concentration of **voriconazole**, also plasma concentration of efavirenz increased (increase voriconazole dose and reduce efavirenz dose); efavirenz possibly reduces plasma concentration of **caspofungin**—consider increasing dose of caspofungin

Antimalarials: efavirenz possibly affects plasma concentration of **proguanil**

- Antipsychotics: efavirenz possibly reduces plasma concentration of **aripiprazole** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); efavirenz possibly increases plasma concentration of **pimozide** (increased risk of ventricular arrhythmias—avoid concomitant use)

- Antivirals: avoidance of efavirenz advised by manufacturer of **atazanavir** (plasma concentration of atazanavir reduced); efavirenz reduces plasma concentration of **darunavir** (adjust dose—consult product literature); efavirenz reduces the plasma concentration of **dolutegravir** (*see* Dose under Dolutegravir, p. 324); avoidance of efavirenz advised by manufacturer of **elvitegravir**; efavirenz possibly reduces plasma concentration of **etravirine**—avoid concomitant use; efavirenz reduces plasma concentration of **indinavir**; efavirenz reduces plasma concentration of **lopinavir**—consider increasing dose of lopinavir; efavirenz possibly reduces plasma concentration of **maraviroc**—consider increasing dose of maraviroc; plasma concentration of efavirenz reduced by **nevirapine**—avoid concomitant use; toxicity of efavirenz

Efavirenz**Antivirals** (*continued*)

virens increased by **ritonavir**, monitor liver function tests —manufacturer of **Atripla**® advises avoid concomitant use with **high-dose** ritonavir; efavirenz significantly reduces plasma concentration of **saquinavir**; efavirenz reduces plasma concentration of **telaprevir**—increase dose of telaprevir

- Anxiolytics and Hypnotics: increased risk of prolonged sedation when efavirenz given with **midazolam**—avoid concomitant use

- Atovaquone: efavirenz reduces plasma concentration of **atovaquone**—avoid concomitant use

Bupropion: efavirenz accelerates metabolism of **bupropion** (reduced plasma concentration)

Calcium-channel Blockers: efavirenz reduces plasma concentration of **diltiazem**

- Ciclosporin: efavirenz possibly reduces plasma concentration of **ciclosporin**

- Cytotoxics: efavirenz possibly reduces plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid concomitant use

- Ergot Alkaloids: increased risk of ergotism when efavirenz given with **ergot alkaloids**—avoid concomitant use

Grapefruit Juice: plasma concentration of efavirenz possibly increased by **grapefruit juice**

Lipid-regulating Drugs: efavirenz reduces plasma concentration of **atorvastatin**, **pravastatin** and **simvastatin**

- Orlistat: absorption of efavirenz possibly reduced by **orlistat**

- Progestogens: efavirenz possibly reduces contraceptive effect of **progestogens**

- Tacrolimus: efavirenz possibly affects plasma concentration of **tacrolimus**

Elvitegravir *see* 5HT₁-receptor Agonists (under HT)

Eltrombopag

Antacids: absorption of eltrombopag reduced by **antacids** (give at least 4 hours apart)

Antivirals: plasma concentration of eltrombopag possibly reduced by **lopinavir**

Calcium Salts: absorption of eltrombopag possibly reduced by **calcium salts** (give at least 4 hours apart)

Dairy Products: absorption of eltrombopag possibly reduced by **dairy products** (give at least 4 hours apart)

Iron: absorption of eltrombopag possibly reduced by **oral iron** (give at least 4 hours apart)

- Lipid-regulating Drugs: eltrombopag increases plasma concentration of **rosuvastatin** (consider reducing dose of rosuvastatin)

Selenium: absorption of eltrombopag possibly reduced by **selenium** (give at least 4 hours apart)

Zinc: absorption of eltrombopag possibly reduced by **zinc** (give at least 4 hours apart)

Elvitegravir

Antacids: absorption of elvitegravir reduced by **antacids** (give at least 4 hours apart)

- Antibacterials: plasma concentration of elvitegravir reduced by **rifabutin** also plasma concentration of active metabolite of rifabutin increased—reduce dose of rifabutin; manufacturer of elvitegravir advises avoid concomitant use with **rifampicin**

- Antidepressants: manufacturer of elvitegravir advises avoid concomitant use with **St John's wort**

- Antiepileptics: manufacturer of elvitegravir advises avoid concomitant use with **carbamazepine**, **phenobarbital** and **phenytoin**

- Antivirals: plasma concentration of elvitegravir increased by **atazanavir** and **lopinavir** boosted with ritonavir (reduce dose of elvitegravir); manufacturer of elvitegravir advises avoid concomitant use with **efavirenz** and **nevirapine**

Elvitegravir (*continued*)

Bosentan: manufacturer of elvitegravir advises avoid concomitant use with **bosentan**

- **Orlistat**: absorption of elvitegravir possibly reduced by **orlistat**

Progestogens: elvitegravir increases plasma concentration of **norgestimate**

Emtricitabine

Antivirals: manufacturer of emtricitabine advises avoid concomitant use with **lamivudine**

- **Orlistat**: absorption of emtricitabine possibly reduced by **orlistat**

Enalapril *see* ACE Inhibitors**Enfuvirtide**

- **Orlistat**: absorption of enfuvirtide possibly reduced by **orlistat**

Enoxaparin *see* Heparins**Enoximone** *see* Phosphodiesterase Inhibitors**Entacapone**

- **Anticoagulants**: entacapone enhances anticoagulant effect of **warfarin**

- **Antidepressants**: manufacturer of entacapone advises caution with **moclobemide**, **tricyclics** and **venlafaxine**; avoid concomitant use of entacapone with non-selective **MAOIs**

Dopaminergics: entacapone possibly enhances effects of **apomorphine**; entacapone possibly reduces plasma concentration of **rasagiline**; manufacturer of entacapone advises max. dose of 10mg **selegiline** if used concomitantly

Iron: absorption of entacapone reduced by **oral iron**

Mementine: effects of dopaminergics possibly enhanced by **mementine**

Methyl dopa: entacapone possibly enhances effects of **methyl dopa**; antiparkinsonian effect of dopaminergics antagonised by **methyl dopa**

Sympathomimetics: entacapone possibly enhances effects of **adrenaline** (epinephrine), **dobutamine**, **dopamine** and **noradrenaline** (norepinephrine)

Enteral Foods

- **Anticoagulants**: the presence of vitamin K in some enteral feeds can antagonise the anticoagulant effect of **coumarins** and **phenindione**

Antiepileptics: enteral feeds possibly reduce absorption of **phenytoin**

Enzalutamide

Antibacterials: manufacturer of enzalutamide advises avoid concomitant use with **rifampicin**

- **Anticoagulants**: enzalutamide possibly reduces plasma concentration of **coumarins**
- **Lipid-regulating Drugs**: plasma concentration of enzalutamide increased by **gemfibrozil**—manufacturer of enzalutamide advises avoid concomitant use or halve dose of enzalutamide

Ephedrine *see* Sympathomimetics**Epinephrine** (adrenaline) *see* Sympathomimetics**Epirubicin**

- **Antipsychotics**: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- **Ciclosporin**: plasma concentration of epirubicin increased by **ciclosporin**
- **Ulcer-healing Drugs**: plasma concentration of epirubicin increased by **cimetidine**

Eplerenone *see* Diuretics**Eprosartan** *see* Angiotensin-II Receptor Antagonists**Eptifibatide**

Iloprost: increased risk of bleeding when eptifibatide given with **iloprost**

Ergometrine *see* Ergot Alkaloids**Ergot Alkaloids**

- **Antibacterials**: increased risk of ergotism when ergotamine given with **macrolides** or **tetrathromycin**—avoid concomitant use; increased risk of ergotism when ergotamine given with **tetracyclines**

Ergot Alkaloids (*continued*)

Antidepressants: possible risk of hypertension when ergotamine given with **reboxetine**

- **Antifungals**: avoidance of ergotamine advised by manufacturer of **itraconazole** (increased risk of ergotism); increased risk of ergotism when ergotamine given with **imidazoles** or **triazoles**—avoid concomitant use
- **Antivirals**: plasma concentration of ergot alkaloids possibly increased by **atazanavir**—avoid concomitant use; avoidance of ergot alkaloids advised by manufacturer of **boceprevir** and **telaprevir**; increased risk of ergotism when ergot alkaloids given with **darunavir**—manufacturer of darunavir advises avoid concomitant use; increased risk of ergotism when ergot alkaloids given with **efavirenz**—avoid concomitant use; increased risk of ergotism when ergotamine given with **fosamprenavir**, **indinavir**, **ritonavir** or **saquinavir**—avoid concomitant use

Beta-blockers: increased peripheral vasoconstriction when ergotamine given with **beta-blockers**

- **Cobicistat**: plasma concentration of ergot alkaloids possibly increased by **cobicistat**—manufacturer of cobicistat advises avoid concomitant use
- **Cytotoxics**: caution with ergot alkaloids advised by manufacturer of **crizotinib**
- **5HT₂-receptor Agonists**: increased risk of vasospasm when ergotamine given with **almotriptan**, **rizatriptan**, **sumatriptan** or **zolmitriptan** (avoid ergotamine for 6 hours after almotriptan, rizatriptan, sumatriptan or zolmitriptan for 24 hours after ergotamine); increased risk of vasospasm when ergotamine given with **eletriptan**, **frovatriptan** or **naratriptan** (avoid ergotamine for 24 hours after eletriptan, frovatriptan or naratriptan, avoid eletriptan, frovatriptan or naratriptan for 24 hours after ergotamine)

Sympathomimetics: increased risk of ergotism when ergotamine given with **sympathomimetics**

- **Ticagrelor**: plasma concentration of ergot alkaloids possibly increased by **ticagrelor**
- **Ulcer-healing Drugs**: increased risk of ergotism when ergotamine given with **cimetidine**—avoid concomitant use

Ergotamine *see* Ergot Alkaloids**Eribulin**

Antibacterials: plasma concentration of eribulin possibly reduced by **rifampicin**

Antidepressants: plasma concentration of eribulin possibly reduced by **St John's wort**

Antiepileptics: plasma concentration of eribulin possibly reduced by **carbamazepine** and **phenytoin**

- **Antipsychotics**: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Erlotinib

- **Analgesics**: increased risk of bleeding when erlotinib given with **NSAIDs**

- **Antacids**: plasma concentration of erlotinib possibly reduced by **antacids**—give antacids at least 4 hours before or 2 hours after erlotinib

Antibacterials: plasma concentration of erlotinib increased by **ciprofloxacin**; metabolism of erlotinib accelerated by **rifampicin** (reduced plasma concentration)

- **Anticoagulants**: increased risk of bleeding when erlotinib given with **coumarins**
- **Antipsychotics**: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- **Antivirals**: avoidance of erlotinib advised by manufacturer of **boceprevir**
- **Cytotoxics**: plasma concentration of erlotinib possibly increased by **capecitabine**
- **Ulcer-healing Drugs**: manufacturer of erlotinib advises avoid concomitant use with **cimetidine**, **esome-**

Erlotinib● Ulcer-healing Drugs (*continued*)

prazole, ●**famotidine**, ●**lansoprazole**, ●**nizatidine**, ●**pantoprazole** and ●**rabeprazole**; plasma concentration of erlotinib reduced by ●**ranitidine**—manufacturer of erlotinib advises give at least 2 hours before or 10 hours after ranitidine; plasma concentration of erlotinib reduced by ●**omeprazole**—manufacturer of erlotinib advises avoid concomitant use

Ertapenem

- Antiepileptics: carbapenems reduce plasma concentration of ●**valproate**—avoid concomitant use
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Erythromycin *see* Macrolides**Escitalopram** *see* Antidepressants, SSRI**Eslicarbazepine**

- Anticoagulants: eslicarbazepine reduces plasma concentration of **warfarin**
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and ●**tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by ●**SSRIs** and ●**tricyclics** (convulsive threshold lowered)

Antiepileptics: plasma concentration of eslicarbazepine possibly reduced by **carbamazepine** but risk of side-effects increased; manufacturer of eslicarbazepine advises avoid concomitant use with **oxcarbazepine**; plasma concentration of eslicarbazepine reduced by **phenytoin**, also plasma concentration of phenytoin increased

- Antimalarials: anticonvulsant effect of antiepileptics antagonised by ●**mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ●**antipsychotics** (convulsive threshold lowered)
- Lipid-regulating Drugs: eslicarbazepine reduces plasma concentration of **rosuvastatin**; eslicarbazepine reduces plasma concentration of **simvastatin**—consider increasing dose of simvastatin

- Oestrogens: eslicarbazepine accelerates metabolism of ●**oestrogens** (reduced contraceptive effect—see p. 402)
- Orlistat: possible increased risk of convulsions when antiepileptics given with ●**orlistat**
- Progestogens: eslicarbazepine accelerates metabolism of ●**progestogens** (reduced contraceptive effect—see p. 402)

Esmolol *see* Beta-blockers**Esomeprazole** *see* Proton Pump Inhibitors**Estradiol** *see* Oestrogens**Estramustine**

Antacids: absorption of estramustine possibly reduced by **aluminium hydroxide** and **oral magnesium salts**—manufacturer of estramustine advises avoid concomitant administration

- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)
- Bisphosphonates: plasma concentration of estramustine increased by ●**sodium clodronate**
- Calcium Salts: absorption of estramustine reduced by **calcium salts** (manufacturer of estramustine advises avoid concomitant administration)

Estriol *see* Oestrogens**Estrone** *see* Oestrogens**Etanercept**

- Abatacept: avoid concomitant use of etanercept with ●**abatacept**
- Anakinra: avoid concomitant use of etanercept with ●**anakinra**
- Vaccines: avoid concomitant use of etanercept with live ●**vaccines** (see p. 604)

Ethinylestradiol *see* Oestrogens**Ethosuximide**

- Antibacterials: metabolism of ethosuximide inhibited by ●**isoniazid** (increased plasma concentration and risk of toxicity)
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and ●**tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by ●**SSRIs** and ●**tricyclics** (convulsive threshold lowered)
- Antiepileptics: plasma concentration of ethosuximide possibly reduced by **carbamazepine** and **phenobarbital**; plasma concentration of ethosuximide possibly reduced by ●**phenytoin**, also plasma concentration of phenytoin possibly increased; plasma concentration of ethosuximide possibly increased by **valproate**
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by ●**mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ●**antipsychotics** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with ●**orlistat**

Etidronate Disodium *see* Bisphosphonates**Etodolac** *see* NSAIDs**Etomidate** *see* Anaesthetics, General**Etonogestrel** *see* Progestogens**Etoposide**

- Anticoagulants: etoposide possibly enhances anticoagulant effect of ●**coumarins**
- Antiepileptics: plasma concentration of etoposide possibly reduced by **phenobarbital** and **phenytoin**
- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)
- Atovaquone: plasma concentration of etoposide possibly increased by **atovaquone**
- Ciclosporin: plasma concentration of etoposide possibly increased by **ciclosporin** (increased risk of toxicity)

Etoricoxib *see* NSAIDs**Etravirine**

- Antibacterials: etravirine reduces plasma concentration of ●**clarithromycin** (but concentration of an active metabolite increased), also plasma concentration of etravirine increased; plasma concentration of both drugs reduced when etravirine given with ●**rifabutin**; manufacturer of etravirine advises avoid concomitant use with **rifampicin**
- Antidepressants: manufacturer of etravirine advises avoid concomitant use with **St John's wort**
- Antiepileptics: manufacturer of etravirine advises avoid concomitant use with **carbamazepine**, **phenobarbital** and **phenytoin**
- Antimalarials: etravirine reduces plasma concentration of **artemether with lumefantrine**
- Antivirals: effects of both drugs possibly reduced when etravirine given with **boceprevir**; etravirine reduces the plasma concentration of ●**dolutegravir** (see Cautions under Dolutegravir, p. 324); plasma concentration of etravirine possibly reduced by ●**efavirenz** and ●**nevirapine**—avoid concomitant use; etravirine increases plasma concentration of ●**fosamprenavir** (consider reducing dose of fosamprenavir); etravirine possibly reduces plasma concentration of ●**indinavir**—avoid concomitant use; etravirine possibly reduces plasma concentration of **maraviroc**; plasma concentration of etravirine reduced by ●**tipranavir**, also plasma concentration of tipranavir increased (avoid concomitant use)
- Cardiac Glycosides: etravirine increases plasma concentration of **digoxin**
- Clopidogrel: etravirine possibly reduces antiplatelet effect of ●**clopidogrel**

Etravirine (*continued*)

- Cytotoxics: etravirine possibly reduces plasma concentration of ●**bosutinib**—manufacturer of bosutinib advises avoid concomitant use
- Lipid-regulating Drugs: etravirine possibly reduces plasma concentration of ●**atorvastatin**
- Orlistat: absorption of etravirine possibly reduced by ●**orlistat**
- Sildenafil: etravirine reduces plasma concentration of **sildenafil**

Everolimus

- Antibacterials: plasma concentration of everolimus possibly increased by ●**clarithromycin** and ●**telithromycin**—manufacturer of everolimus advises avoid concomitant use; plasma concentration of everolimus increased by ●**erythromycin** (consider reducing the dose of everolimus—consult everolimus product literature); plasma concentration of everolimus reduced by ●**rifampicin** (avoid concomitant use or consider increasing the dose of everolimus—consult everolimus product literature)
- Antidepressants: plasma concentration of everolimus possibly reduced by **St John's wort**—manufacturer of everolimus advises avoid concomitant use
- Antifungals: plasma concentration of everolimus possibly increased by ●**itraconazole**, ●**posaconazole** and ●**voriconazole**—manufacturer of everolimus advises avoid concomitant use
- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)
- Antivirals: plasma concentration of everolimus possibly increased by ●**atazanavir**, ●**darunavir**, ●**indinavir**, ●**ritonavir** and ●**sacquinavir**—manufacturer of everolimus advises avoid concomitant use
- Calcium-channel Blockers: plasma concentration of both drugs may increase when everolimus given with ●**verapamil** (consider reducing the dose of everolimus—consult everolimus product literature)
- Ciclosporin: plasma concentration of everolimus increased by ●**ciclosporin** (consider reducing the dose of everolimus—consult everolimus product literature)
- Cytotoxics: plasma concentration of everolimus increased by ●**imatinib** (consider reducing the dose of everolimus—consult everolimus product literature)
- Grapefruit Juice: manufacturer of everolimus advises avoid concomitant use with **grapefruit juice**

Exemestane

Antibacterials: plasma concentration of exemestane possibly reduced by **rifampicin**

Exenatide *see* Antidiabetics**Ezetimibe**

- Anticoagulants: ezetimibe possibly enhances anticoagulant effect of ●**coumarins**
- Ciclosporin: plasma concentration of both drugs may increase when ezetimibe given with ●**ciclosporin**
- Lipid-regulating Drugs: increased risk of cholelithiasis and gallbladder disease when ezetimibe given with **fibrates**—discontinue if suspected

Famciclovir

Probenecid: excretion of famciclovir possibly reduced by ●**probenecid** (increased plasma concentration)

Famotidine *see* Histamine H₂-antagonists**Fampridine**

- Ulcer-healing Drugs: manufacturer of fampridine advises avoid concomitant use with ●**cimetidine**

Febuxostat

- Azathioprine: manufacturer of febuxostat advises avoid concomitant use with ●**azathioprine**
- Cytotoxics: manufacturer of febuxostat advises avoid concomitant use with ●**mercaptopurine**

Felodipine *see* Calcium-channel Blockers**Fenofibrate** *see* Fibrates**Fenoprofen** *see* NSAIDs**Fentanyl** *see* Opioid Analgesics**Ferrous Salts** *see* Iron**Fesoterodine** *see* Antimuscarinics**Fexofenadine** *see* Antihistamines**Fibrates**

- Antibacterials: increased risk of myopathy when fibrates given with ●**daptomycin** (preferably avoid concomitant use)
- Anticoagulants: fibrates enhance anticoagulant effect of ●**coumarins** and ●**phenindione**
- Antidiabetics: fibrates may improve glucose tolerance and have an additive effect with **insulin** or **sulfonylureas**; gemfibrozil possibly enhances hypoglycaemic effect of **nateglinide**; increased risk of severe hypoglycaemia when gemfibrozil given with ●**repaglinide**—avoid concomitant use
- Ciclosporin: increased risk of renal impairment when bezafibrate or fenofibrate given with **ciclosporin**
- Colchicine: possible increased risk of myopathy when fibrates given with ●**colchicine**
- Cytotoxics: gemfibrozil increases plasma concentration of ●**bexarotene**—avoid concomitant use
- Hormone Antagonists: gemfibrozil increases plasma concentration of ●**enzalutamide**—manufacturer of enzalutamide advises avoid concomitant use or halve dose of enzalutamide
- Leukotriene Receptor Antagonists: gemfibrozil increases plasma concentration of **montelukast**
- Lipid-regulating Drugs: increased risk of myopathy when gemfibrozil given with ●**atorvastatin**, ●**fluvastatin** or ●**pravastatin** (preferably avoid concomitant use); increased risk of myopathy when fibrates given with ●**rosuvastatin** (see Dose under Rosuvastatin, p. 126); possible increased risk of myopathy when bezafibrate and ciprofibrate given with ●**simvastatin** (see Dose under Simvastatin, p. 126); increased risk of myopathy when gemfibrozil given with ●**simvastatin** (avoid concomitant use); increased risk of cholelithiasis and gallbladder disease when fibrates given with **ezetimibe**—discontinue if suspected; reduce maximum dose of fenofibrate when given with **statins**—see Dose under Fenofibrate, p. 128; increased risk of myopathy when fibrates given with ●**statins**

Fidaxomicin

Anti-arrhythmics: manufacturer of fidaxomicin advises avoid concomitant use with **amiodarone** and **dronedarone**

Antibacterials: manufacturer of fidaxomicin advises avoid concomitant use with **clarithromycin** and **erythromycin**

Calcium-channel Blockers: manufacturer of fidaxomicin advises avoid concomitant use with **verapamil**

Ciclosporin: manufacturer of fidaxomicin advises avoid concomitant use with **ciclosporin**

Filgrastim

Note Pegfilgrastim interactions as for filgrastim

Cytotoxics: neutropenia possibly exacerbated when filgrastim given with **fluorouracil**

Fingolimod

- Anti-arrhythmics: possible increased risk of bradycardia when fingolimod given with ●**amiodarone**, ●**dipyridamide** or **dronedarone**
- Beta-blockers: possible increased risk of bradycardia when fingolimod given with ●**beta-blockers**
- Calcium-channel Blockers: possible increased risk of bradycardia when fingolimod given with ●**diltiazem** or ●**verapamil**

Flavoxate *see* Antimuscarinics**Flecainide**

Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with **bupivacaine**, **levobupivacaine**, **prilocaine** or **ropivacaine**

- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other ●**anti-**

Flecainide

- Anti-arrhythmics (*continued*)
 - **arrhythmics**; plasma concentration of flecainide increased by **amiodarone** (halve dose of flecainide)
 - Antidepressants: plasma concentration of flecainide increased by **fluoxetine**; increased risk of ventricular arrhythmias when flecainide given with **tricyclics**
 - Antihistamines: increased risk of ventricular arrhythmias when flecainide given with **mizolastine**—avoid concomitant use
 - Antimalarials: avoidance of flecainide advised by manufacturer of **artemether with lumefantrine** (risk of ventricular arrhythmias); plasma concentration of flecainide increased by **quinine**
 - Antimuscarinics: increased risk of ventricular arrhythmias when flecainide given with **tolterodine**
 - Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with **antipsychotics** that prolong the QT interval; increased risk of arrhythmias when flecainide given with **clozapine**
 - Antivirals: plasma concentration of flecainide possibly increased by **fosamprenavir**, **indinavir**, **lopinavir** and **ritonavir** (increased risk of ventricular arrhythmias—avoid concomitant use); increased risk of ventricular arrhythmias when flecainide given with **saquinavir**—avoid concomitant use; caution with flecainide advised by manufacturer of **telaprevir** (risk of ventricular arrhythmias)
 - Beta-blockers: increased risk of myocardial depression and bradycardia when flecainide given with **beta-blockers**; increased myocardial depression when anti-arrhythmics given with **beta-blockers**
 - Calcium-channel Blockers: increased risk of myocardial depression and asystole when flecainide given with **verapamil**
 - Diuretics: increased cardiac toxicity with flecainide if hypokalaemia occurs with **acetazolamide**, **loop diuretics** or **thiazides and related diuretics**
- Ulcer-healing Drugs: metabolism of flecainide inhibited by **cimetidine** (increased plasma concentration)

Flucloxacillin *see* Penicillins

Fluconazole *see* Antifungals, Triazole

Flucytosine

Antifungals: renal excretion of flucytosine decreased and cellular uptake increased by **amphotericin** (toxicity possibly increased)

Cytotoxics: plasma concentration of flucytosine possibly reduced by **cytarabine**

Fludarabine

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
 - Cytotoxics: fludarabine increases intracellular concentration of **cytarabine**; increased pulmonary toxicity when fludarabine given with **pentostatin** (unacceptably high incidence of fatalities)
- Dipyridamole: effects of fludarabine possibly reduced by **dipyridamole**

Fludrocortisone *see* Corticosteroids

Fluorides

Calcium Salts: absorption of fluorides reduced by calcium salts

Fluorouracil

Note Capecitabine is a prodrug of fluorouracil

Note Tegafur is a prodrug of fluorouracil

- Allopurinol: manufacturer of capecitabine advises avoid concomitant use with **allopurinol**
- Antibacterials: metabolism of fluorouracil inhibited by **metronidazole** (increased toxicity)
- Anticoagulants: fluorouracil enhances anticoagulant effect of **coumarins**
- Antiepileptics: fluorouracil possibly inhibits metabolism of **phenytoin** (increased risk of toxicity)
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Fluorouracil (*continued*)

Cytotoxics: capecitabine possibly increases plasma concentration of **erlotinib**

Filgrastim: neutropenia possibly exacerbated when fluorouracil given with **filgrastim**

- Temoporfin: increased skin photosensitivity when topical fluorouracil used with **temoporfin**

Ulcer-healing Drugs: metabolism of fluorouracil inhibited by **cimetidine** (increased plasma concentration)

Fluoxetine *see* Antidepressants, SSRI

Flupentixol *see* Antipsychotics

Fluphenazine *see* Antipsychotics

Flurazepam *see* Anxiolytics and Hypnotics

Flurbiprofen *see* NSAIDs

Flutamide

- Anticoagulants: flutamide enhances anticoagulant effect of **coumarins**

Fluticasone *see* Corticosteroids

Fluvastatin *see* Statins

Fluvoxamine *see* Antidepressants, SSRI

Folates

Aminosalicylates: absorption of folic acid possibly reduced by **sulfasalazine**

Antiepileptics: folates possibly reduce plasma concentration of **phenobarbital** and **phenytoin**

- Cytotoxics: avoidance of folates advised by manufacturer of **alitrexed**

Folic Acid *see* Folates

Folinic Acid *see* Folates

Formoterol *see* Sympathomimetics, Beta₂

Fosamprenavir

Note Fosamprenavir is a prodrug of amprenavir

Analgesics: fosamprenavir reduces plasma concentration of **methadone**

- Anti-arrhythmics: fosamprenavir possibly increases plasma concentration of **amiodarone**, **flecainide** and **propafenone** (increased risk of ventricular arrhythmias—avoid concomitant use); fosamprenavir possibly increases plasma concentration of **lidocaine**—avoid concomitant use

- Antibacterials: fosamprenavir increases plasma concentration of **rifabutin** (reduce dose of rifabutin); plasma concentration of fosamprenavir significantly reduced by **rifampicin**—avoid concomitant use; avoidance of concomitant fosamprenavir in severe renal and hepatic impairment advised by manufacturer of **telithromycin**

Anticoagulants: avoidance of fosamprenavir advised by manufacturer of **apixaban** and **rivaroxaban**; fosamprenavir may enhance or reduce anticoagulant effect of **coumarins**

- Antidepressants: plasma concentration of fosamprenavir reduced by **St John's wort**—avoid concomitant use

Antiepileptics: plasma concentration of fosamprenavir possibly reduced by **carbamazepine** and **phenobarbital**

Antifungals: plasma concentration of both drugs may increase when fosamprenavir given with **itraconazole**; fosamprenavir possibly reduces plasma concentration of **posaconazole**

- Antimalarials: caution with fosamprenavir advised by manufacturer of **artemether with lumefantrine**; fosamprenavir possibly increases plasma concentration of **quinine** (increased risk of toxicity)

Antimuscarinics: avoidance of fosamprenavir advised by manufacturer of **darifenacin** and **tolterodine**

- Antipsychotics: fosamprenavir possibly increases plasma concentration of **aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); fosamprenavir increases plasma concentration of **pimozide** (increased risk of ventricular arrhythmias—avoid concomitant use); fosamprenavir possibly increases plasma concentration of **quetia-**

Fosamprenavir

- Antipsychotics (*continued*)
pine—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: manufacturer of fosamprenavir advises avoid concomitant use with ●**boceprevir** and ●**raltegravir**; fosamprenavir reduces plasma concentration of ●**adolutegravir**; plasma concentration of fosamprenavir increased by ●**etravirine** (consider reducing dose of fosamprenavir); plasma concentration of fosamprenavir reduced by ●**lopinavir**, effect on lopinavir plasma concentration not predictable—avoid concomitant use; plasma concentration of fosamprenavir reduced by ●**maraviroc**—avoid concomitant use; plasma concentration of fosamprenavir possibly reduced by ●**nevirapine**—avoid unboosted fosamprenavir; manufacturers advise avoid concomitant use of fosamprenavir with ●**telaprevir**; plasma concentration of fosamprenavir reduced by ●**tipranavir**
- Anxiolytics and Hypnotics: fosamprenavir possibly increases plasma concentration of ●**midazolam** (risk of prolonged sedation—avoid concomitant use of oral midazolam)
- Ciclosporin: fosamprenavir increases plasma concentration of ●**ciclosporin**
- Cytotoxics: fosamprenavir possibly increases the plasma concentration of ●**bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Dapoxetine: manufacturer of dapoxetine advises dose reduction when fosamprenavir given with ●**dapoxetine** (see Dose under Dapoxetine, BNF section 7.4.6)
- Ergot Alkaloids: increased risk of ergotism when fosamprenavir given with ●**ergotamine**—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when fosamprenavir given with ●**atorvastatin**; possible increased risk of myopathy when fosamprenavir given with ●**rosuvastatin**—manufacturer of rosuvastatin advises avoid concomitant use; possible increased risk of myopathy when fosamprenavir given with ●**simvastatin**—avoid concomitant use; avoidance of fosamprenavir advised by manufacturer of ●**lomitapide** (plasma concentration of lomitapide possibly increased)
- Orlistat: absorption of fosamprenavir possibly reduced by ●**orlistat**
- Ranolazine: fosamprenavir possibly increases plasma concentration of ●**ranolazine**—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: fosamprenavir possibly increases plasma concentration of ●**sildenafil**
- Tacrolimus: fosamprenavir increases plasma concentration of ●**tacrolimus**
- Tadalafil: fosamprenavir possibly increases plasma concentration of ●**tadalafil**
- Vardenafil: fosamprenavir possibly increases plasma concentration of ●**vardenafil**

Fosaprepitant *see* Aprepitant

Foscarnet

- Pentamidine Isetionate: increased risk of hypocalcaemia when foscarnet given with *parenteral* ●**pentamidine isetionate**

Fosinopril *see* ACE Inhibitors

Fosphenytoin *see* Phenytoin

Framycetin *see* Aminoglycosides

Frovatriptan *see* 5HT₁-receptor Agonists (under HT)

Furosemide *see* Diuretics

Fusidic Acid

- Antivirals: plasma concentration of both drugs increased when fusidic acid given with ●**ritonavir**—avoid concomitant use; plasma concentration of

Fusidic Acid

- Antivirals (*continued*)
 both drugs may increase when fusidic acid given with ●**squinavir**
- Lipid-regulating Drugs: risk of myopathy and rhabdomyolysis when fusidic acid given with ●**statins**—avoid concomitant use and for 7 days after last fusidic acid dose
 Sugammadex: fusidic acid possibly reduces response to ●**sugammadex**
 Vaccines: antibacterials inactivate ●**oral typhoid vaccine**—*see* p. 626

Gabapentin

- Analgesics: bioavailability of gabapentin increased by ●**morphine**
- Antacids: absorption of gabapentin reduced by ●**antacids**
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by ●**MAOIs** and ●**tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by ●**SSRIs** and ●**tricyclics** (convulsive threshold lowered)
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by ●**mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ●**antipsychotics** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with ●**orlistat**

Galantamine *see* Parasympathomimetics

Ganciclovir

- Note** Increased risk of myelosuppression with other myelosuppressive drugs—consult product literature
- Note** Valganciclovir interactions as for ganciclovir
- Antibacterials: increased risk of convulsions when ganciclovir given with ●**imipenem with cilastatin**
- Antivirals: ganciclovir possibly increases plasma concentration of ●**didanosine**; profound myelosuppression when ganciclovir given with ●**zidovudine** (if possible avoid concomitant administration, particularly during initial ganciclovir therapy)
 Mycophenolate: plasma concentration of ganciclovir possibly increased by ●**mycophenolate**, also plasma concentration of inactive metabolite of mycophenolate possibly increased
 Probenecid: excretion of ganciclovir reduced by ●**probenecid** (increased plasma concentration and risk of toxicity)
 Tacrolimus: possible increased risk of nephrotoxicity when ganciclovir given with ●**tacrolimus**

Gefitinib

- Antibacterials: plasma concentration of gefitinib reduced by ●**rifampicin**—avoid concomitant use
- Anticoagulants: gefitinib possibly enhances anticoagulant effect of ●**warfarin**
- Antidepressants: manufacturer of gefitinib advises avoid concomitant use with ●**St John's wort**
- Antiepileptics: manufacturer of gefitinib advises avoid concomitant use with ●**carbamazepine**, ●**phenobarbital** and ●**phenytoin**
- Antifungals: plasma concentration of gefitinib increased by ●**itraconazole**
- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)
- Antivirals: avoidance of gefitinib advised by manufacturer of ●**boceprevir**
- Ulcer-healing Drugs: plasma concentration of gefitinib reduced by ●**ranitidine**

Gemcitabine

Anticoagulants: gemcitabine possibly enhances anticoagulant effect of ●**warfarin**

- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)

Gemeprost *see* Prostaglandins

Gemfibrozil *see* Fibrates

Gentamicin *see* Aminoglycosides

Gestodene *see* Progestogens

Glibenclamide *see* Antidiabetics

Gliclazide *see* Antidiabetics

Glimepiride *see* Antidiabetics

Glipizide *see* Antidiabetics

Glucosamine

- Anticoagulants: glucosamine enhances anticoagulant effect of **warfarin** (avoid concomitant use)

Glyceryl Trinitrate *see* Nitrates

Glycopyrronium *see* Antimuscarinics

Gold *see* Sodium Aurothiomalate

Golimimumab

- Abatacept: avoid concomitant use of golimumab with **abatacept**
- Anakinra: avoid concomitant use of golimumab with **anakinra**
- Vaccines: avoid concomitant use of golimumab with live **vaccines** (see p. 604)

Grapefruit Juice

- Aliskiren: grapefruit juice reduces plasma concentration of **aliskiren**—avoid concomitant use
- Anti-arrhythmics: grapefruit juice increases plasma concentration of **amiodarone**; grapefruit juice increases plasma concentration of **dronedarone**—avoid concomitant use
- Antidepressants: grapefruit juice possibly increases plasma concentration of **sertraline**
- Antihistamines: grapefruit juice reduces plasma concentration of **bilastine**; grapefruit juice increases plasma concentration of **rupatadine**—avoid concomitant use

Antimalarials: avoidance of grapefruit juice advised by manufacturer of **piperazine with arteminol**; grapefruit juice possibly increases plasma concentration of **artemether with lumefantrine**

- Antipsychotics: grapefruit juice possibly increases plasma concentration of **quetiapine**—manufacturer of quetiapine advises avoid concomitant use

Antivirals: grapefruit juice possibly increases plasma concentration of **efavirenz**

Anxiolytics and Hypnotics: grapefruit juice possibly increases plasma concentration of **oral midazolam**; grapefruit juice increases plasma concentration of **bupirone**

Calcium-channel Blockers: grapefruit juice possibly increases plasma concentration of **amlodipine**; grapefruit juice increases plasma concentration of **felodipine**, **lacidipine**, **lercanidipine**, **nicardipine**, **nifedipine**, **nimodipine** and **verapamil**

- Ciclosporin: grapefruit juice increases plasma concentration of **ciclosporin** (increased risk of toxicity)
- Colchicine: grapefruit juice possibly increases risk of **colchicine** toxicity

- Cytotoxics: grapefruit juice possibly increases plasma concentration of **axitinib**; grapefruit juice possibly increases the plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; grapefruit juice possibly increases plasma concentration of **crizotinib** and **vinflunine**—manufacturer of crizotinib and vinflunine advises avoid concomitant use; avoidance of grapefruit juice advised by manufacturer of **everolimus**, **lapatinib**, **nilotinib** and **pazopanib**

Ivabradine: grapefruit juice increases plasma concentration of **ivabradine**

Ivacaftor: grapefruit juice possibly increases plasma concentration of **ivacaftor**—manufacturer of ivacaftor advises avoid concomitant use

- Lipid-regulating Drugs: grapefruit juice possibly increases plasma concentration of **atorvastatin**; grapefruit juice increases plasma concentration of **simvastatin**—avoid concomitant use; avoidance of grapefruit juice advised by manufacturer of **lomitapide**

Grapefruit Juice (*continued*)

Pirfenidone: avoidance of grapefruit juice advised by manufacturer of **pirfenidone**

- Ranolazine: grapefruit juice possibly increases plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: grapefruit juice possibly increases plasma concentration of **sildenafil**
- Sirolimus: grapefruit juice increases plasma concentration of **sirolimus**—avoid concomitant use
- Tacrolimus: grapefruit juice increases plasma concentration of **tacrolimus**
- Tadalafil: grapefruit juice possibly increases plasma concentration of **tadalafil**
- Tolvaptan: grapefruit juice increases plasma concentration of **tolvaptan**—avoid concomitant use
- Ulipristal: avoidance of grapefruit juice advised by manufacturer of **ulipristal**
- Vardenafil: grapefruit juice possibly increases plasma concentration of **vardenafil**—avoid concomitant use

Griseofulvin

Alcohol: griseofulvin possibly enhances effects of **alcohol**

- Anticoagulants: griseofulvin reduces anticoagulant effect of **coumarins**

Antiepileptics: absorption of griseofulvin reduced by **phenobarbital** (reduced effect)

Ciclosporin: griseofulvin possibly reduces plasma concentration of **ciclosporin**

Oestrogens: anecdotal reports of contraceptive failure and menstrual irregularities when griseofulvin given with **oestrogens**

Progestogens: anecdotal reports of contraceptive failure and menstrual irregularities when griseofulvin given with **progestogens**

Guanethidine *see* Adrenergic Neurone Blockers

Haloperidol *see* Antipsychotics

Heparin *see* Heparins

Heparins

ACE Inhibitors: increased risk of hyperkalaemia when heparins given with **ACE inhibitors**

Aliskiren: increased risk of hyperkalaemia when heparins given with **aliskiren**

- Analgesics: possible increased risk of bleeding when heparins given with **NSAIDs**; increased risk of haemorrhage when anticoagulants given with *intravenous* **diclofenac** (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with **ketorolac** (avoid concomitant use, including low-dose heparins); anticoagulant effect of heparins enhanced by **aspirin**

Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when heparins given with **angiotensin-II receptor antagonists**

- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with **apixaban**, **dabigatran** and **rivaroxaban** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Clopidogrel: increased risk of bleeding when heparins given with **clopidogrel**

Dipyridamole: anticoagulant effect of heparins enhanced by **dipyridamole**

Iloprost: anticoagulant effect of heparins possibly enhanced by **iloprost**

- Nitrates: anticoagulant effect of heparins reduced by *infusion of* **glyceryl trinitrate**

Histamine

Antidepressants: manufacturer of histamine advises avoid concomitant use with **MAOIs**; effects of histamine theoretically antagonised by **tricyclics**—manufacturer of histamine advises avoid concomitant use

Histamine (*continued*)

- Antihistamines: effects of histamine theoretically antagonised by **antihistamines**—manufacturer of histamine advises avoid concomitant use
- Antimalarials: manufacturer of histamine advises avoid concomitant use with **antimalarials**
- Antipsychotics: effects of histamine theoretically antagonised by **antipsychotics**—manufacturer of histamine advises avoid concomitant use
- Atovaquone: manufacturer of histamine advises avoid concomitant use with **atovaquone**
- Clonidine: manufacturer of histamine advises avoid concomitant use with **clonidine**
- Corticosteroids: manufacturer of histamine advises avoid concomitant use with **corticosteroids**
- Ulcer-healing Drugs: effects of histamine theoretically antagonised by **histamine H₂-antagonists**—manufacturer of histamine advises avoid concomitant use

Histamine H₂-antagonists

- Alpha-blockers: cimetidine and ranitidine antagonise effects of **•tolazoline**
- Analgesics: cimetidine inhibits metabolism of **opioid analgesics** (increased plasma concentration)
- Anti-arrhythmics: cimetidine increases plasma concentration of **amiodarone** and **•propafenone**; cimetidine inhibits metabolism of **flecainide** (increased plasma concentration); cimetidine increases plasma concentration of **•lidocaine** (increased risk of toxicity)
- Antibacterials: cimetidine increases plasma concentration of **erythromycin** (increased risk of toxicity, including deafness); cimetidine inhibits metabolism of **metronidazole** (increased plasma concentration); metabolism of cimetidine accelerated by **rifampicin** (reduced plasma concentration)
- Anticoagulants: cimetidine inhibits metabolism of **•coumarins** (enhanced anticoagulant effect)
- Antidepressants: cimetidine increases plasma concentration of **citalopram**, **escitalopram**, **mirtazapine** and **sertraline**; cimetidine inhibits metabolism of **amitriptyline**, **doxepin**, **imipramine** and **nortriptyline** (increased plasma concentration); cimetidine increases plasma concentration of **moclobemide** (halve dose of moclobemide); cimetidine possibly increases plasma concentration of **tricyclics**
- Antidiabetics: cimetidine reduces excretion of **metformin** (increased plasma concentration); cimetidine enhances hypoglycaemic effect of **sulfonylureas**
- Anti epileptics: cimetidine inhibits metabolism of **•carbamazepine**, **•phenytoin** and **•valproate** (increased plasma concentration)
- Antifungals: histamine H₂-antagonists reduce absorption of **itraconazole**; avoidance of histamine H₂-antagonists advised by manufacturer of **posaconazole** (plasma concentration of posaconazole possibly reduced); cimetidine reduces plasma concentration of **•posaconazole**; cimetidine increases plasma concentration of **terbinafine**
- Antihistamines: manufacturer of loratadine advises cimetidine possibly increases plasma concentration of **loratadine**; cimetidine increases plasma concentration of **hydroxyzine**
- Antimalarials: avoidance of cimetidine advised by manufacturer of **•artemether with lumefantrine**; cimetidine inhibits metabolism of **chloroquine** and **hydroxychloroquine** and **quinine** (increased plasma concentration)
- Antipsychotics: cimetidine possibly enhances effects of **antipsychotics**, **chlorpromazine** and **clozapine**
- Antivirals: famotidine and ranitidine reduce the plasma concentration of **•atazanavir** (adjust doses of both drugs—consult atazanavir product literature); manufacturer of atazanavir advises adjust doses of both drugs when cimetidine and nizatidine given with **atazanavir**—consult atazanavir product literature; famotidine increases plasma concentration of **raltegravir**; avoidance of histamine H₂-antagonists for 12 hours before or 4 hours after **rilpivirine** advised by manufacturer of rilpivirine—consult product literature; cimetidine possibly increases plasma concentration of **saquinavir**
- Antipsychotics and Hypnotics: cimetidine inhibits metabolism of **benzodiazepines**, **clomethiazole** and **zaleplon** (increased plasma concentration); cimetidine increases plasma concentration of **melatonin**
- Beta-blockers: cimetidine increases plasma concentration of **labetalol**, **metoprolol** and **propranolol**
- Caffeine citrate: cimetidine increases plasma concentration of **caffeine citrate**
- Calcium-channel Blockers: cimetidine possibly inhibits metabolism of **calcium-channel blockers** (increased plasma concentration)
- Ciclosporin: cimetidine possibly increases plasma concentration of **•ciclosporin**
- Clopidogrel: cimetidine possibly reduces antiplatelet effect of **•clopidogrel**
- Cytotoxics: cimetidine possibly enhances myelosuppressive effects of **•carmustine** and **•lomustine**; cimetidine increases plasma concentration of **•epirubicin**; cimetidine inhibits metabolism of **fluorouracil** (increased plasma concentration); famotidine possibly reduces plasma concentration of **dasatinib**; avoidance of cimetidine, famotidine and nizatidine advised by manufacturer of **•erlotinib**; ranitidine reduces plasma concentration of **•erlotinib**—manufacturer of erlotinib advises give at least 2 hours before or 10 hours after ranitidine; ranitidine reduces plasma concentration of **•gefatinib**; histamine H₂-antagonists possibly reduce absorption of **lapatinib**; histamine H₂-antagonists possibly reduce absorption of **pazopanib**—manufacturer of pazopanib advises give at least 2 hours before or 10 hours after histamine H₂-antagonists
- Dopaminergics: cimetidine reduces excretion of **pramipexole** (increased plasma concentration)
- Ergot Alkaloids: increased risk of ergotism when cimetidine given with **•ergotamine**—avoid concomitant use
- Fampridine: avoidance of cimetidine advised by manufacturer of **•fampridine**
- Histamine: histamine H₂-antagonists theoretically antagonise effects of **histamine**—manufacturer of histamine advises avoid concomitant use
- Hormone Antagonists: absorption of cimetidine possibly delayed by **octreotide**
- 5HT₂-receptor Agonists: cimetidine inhibits metabolism of **zolmitriptan** (reduce dose of zolmitriptan)
- Lipid-regulating Drugs: manufacturer of lomitapide advises dose reduction when cimetidine given with **lomitapide** (see Dose under Lomitapide, BNF section 2.12)
- Meibendazole: cimetidine possibly inhibits metabolism of **mebendazole** (increased plasma concentration)
- Roflumilast: cimetidine inhibits the metabolism of **roflumilast**
- Sildenafil: cimetidine increases plasma concentration of **sildenafil** (consider reducing dose of sildenafil)
- Theophylline: cimetidine inhibits metabolism of **•theophylline** (increased plasma concentration)
- Thyroid Hormones: cimetidine reduces absorption of **levothyroxine**
- Ulipristal: avoidance of histamine H₂-antagonists advised by manufacturer of **high-dose •ulipristal** (contraceptive effect of ulipristal possibly reduced)

Homatropine *see* Antimuscarinics

Hormone Antagonists *see* Abiraterone, Bicalutamide, Danazol, Dutasteride, Enzalutamide, Exemestane, Flutamide, Lanreotide, Octreotide, Pasireotide, Tamoxifen, and Toremifene

5HT₁-receptor Agonists

- **Antibacterials:** plasma concentration of eletriptan increased by **●clarithromycin** and **●erythromycin** (risk of toxicity)—avoid concomitant use; metabolism of zolmitriptan possibly inhibited by **quinolones** (reduce dose of zolmitriptan)
- **Antidepressants:** increased risk of CNS toxicity when 5HT₁ agonists given with **●citalopram** (manufacturer of citalopram advises avoid concomitant use); increased risk of CNS toxicity when sumatriptan given with **●citalopram**, **●escitalopram**, **●fluoxetine**, **●fluvoxamine** or **●paroxetine**; metabolism of frovatriptan inhibited by **fluvoxamine**; metabolism of zolmitriptan possibly inhibited by **fluvoxamine** (reduce dose of zolmitriptan); CNS toxicity reported when sumatriptan given with **sertraline**; possible increased serotonergic effects when 5HT₁ agonists given with **duloxetine** or **venlafaxine**; risk of CNS toxicity when zolmitriptan given with **●MAOIs** or **●moclobemide** (reduce dose of zolmitriptan); risk of CNS toxicity when rizatriptan or sumatriptan given with **●MAOIs** (avoid rizatriptan or sumatriptan for 2 weeks after MAOIs); risk of CNS toxicity when rizatriptan or sumatriptan given with **●moclobemide** (avoid rizatriptan or sumatriptan for 2 weeks after moclobemide); possible increased serotonergic effects when naratriptan given with **SSRIs**; increased serotonergic effects when 5HT₁ agonists given with **●St John's wort**—avoid concomitant use
- **Antifungals:** plasma concentration of eletriptan increased by **●itraconazole** (risk of toxicity)—avoid concomitant use
- **Antivirals:** plasma concentration of eletriptan increased by **●indinavir** and **●ritonavir** (risk of toxicity)—avoid concomitant use

Beta-blockers: plasma concentration of rizatriptan increased by **propranolol** (manufacturer of rizatriptan advises halve dose and avoid within 2 hours of propranolol)

- **Dapoxetine:** possible increased risk of serotonergic effects when 5HT₁ agonists given with **●dapoxetine** (manufacturer of dapoxetine advises 5HT₁ agonists should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping 5HT₁ agonists)

Dopaminergics: avoidance of 5HT₁ agonists advised by manufacturer of **selegiline**

- **Ergot Alkaloids:** increased risk of vasospasm when almotriptan, rizatriptan, sumatriptan or zolmitriptan given with **●ergotamine** (avoid ergotamine for 6 hours after almotriptan, rizatriptan, sumatriptan or zolmitriptan, avoid almotriptan, rizatriptan, sumatriptan or zolmitriptan for 24 hours after ergotamine); increased risk of vasospasm when eletriptan, frovatriptan or naratriptan given with **●ergotamine** (avoid ergotamine for 24 hours after eletriptan, frovatriptan or naratriptan, avoid eletriptan, frovatriptan or naratriptan for 24 hours after ergotamine)

Lithium: possible risk of toxicity when sumatriptan given with **lithium**

Ulcer-healing Drugs: metabolism of zolmitriptan inhibited by **cimetidine** (reduce dose of zolmitriptan)

5HT₂-receptor Antagonists

Analgesics: ondansetron possibly antagonises effects of **tramadol**

- **Antibacterials:** metabolism of ondansetron accelerated by **rifampicin** (reduced effect)
- **Antiepileptics:** metabolism of ondansetron accelerated by **carbamazepine** and **phenytoin** (reduced effect)
- **Cytotoxics:** increased risk of ventricular arrhythmias when ondansetron given with **●vandetanib**—avoid concomitant use
- **Dopaminergics:** possible increased hypotensive effect when ondansetron given with **●apomorphine**—avoid concomitant use

Hydralazine *see* Vasodilator Antihypertensives

Hydrochlorothiazide *see* Diuretics

Hydrocortisone *see* Corticosteroids

Hydroflumethiazide *see* Diuretics

Hydromorphone *see* Opioid Analgesics

Hydroxalcite *see* Antacids

Hydroxocobalamin

Antibacterials: response to hydroxocobalamin reduced by **chloramphenicol**

Hydroxycarbamide

- **Antipsychotics:** avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)
- **Antivirals:** increased risk of toxicity when hydroxycarbamide given with **●didanosine** and **●stavudine**—avoid concomitant use

Hydroxychloroquine *see* Chloroquine and Hydroxychloroquine

Hydroxyzine *see* Antihistamines

Hyosine *see* Antimuscarinics

Ibandronic Acid *see* Bisphosphonates

Ibuprofen *see* NSAIDs

Idarubicin

- **Antipsychotics:** avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)
- **Ciclosporin:** plasma concentration of idarubicin increased by **●ciclosporin**

Ifosfamide

- **Anticoagulants:** ifosfamide possibly enhances anticoagulant effect of **●coumarins**
 - **Antipsychotics:** avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)
- Cytotoxics: increased risk of toxicity when ifosfamide given with **cisplatin**

Iloprost

Analgesics: increased risk of bleeding when iloprost given with **NSAIDs** or **aspirin**

Anticoagulants: iloprost possibly enhances anticoagulant effect of **●coumarins** and **heparins**; increased risk of bleeding when iloprost given with **phenindione**

Clopidogrel: increased risk of bleeding when iloprost given with **clopidogrel**

Eptifibatide: increased risk of bleeding when iloprost given with **eptifibatide**

Tirofiban: increased risk of bleeding when iloprost given with **tirofiban**

Imatinib

Analgesics: manufacturer of imatinib advises caution with **paracetamol**

- **Antibacterials:** plasma concentration of imatinib reduced by **●rifampicin**—avoid concomitant use
- **Anticoagulants:** manufacturer of imatinib advises replacement of **warfarin** with a heparin (possibility of enhanced warfarin effect)
- **Antidepressants:** plasma concentration of imatinib reduced by **●St John's wort**—avoid concomitant use
- **Antiepileptics:** plasma concentration of imatinib reduced by **●carbamazepine**, **●oxcarbazepine** and **●phenytoin**—avoid concomitant use
- **Antipsychotics:** avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)
- **Antivirals:** avoidance of imatinib advised by manufacturer of **●boceprevir**
- **Ciclosporin:** imatinib possibly increases plasma concentration of **ciclosporin**
- **Cytotoxics:** imatinib possibly increases the plasma concentration of **●bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; imatinib increases plasma concentration of **●everolimus** (consider reducing the dose of everolimus—consult everolimus product literature)
- **Lipid-regulating Drugs:** imatinib increases plasma concentration of **simvastatin**

Imatinib (*continued*)

Tacrolimus: imatinib increases plasma concentration of **tacrolimus**

Thyroid Hormones: imatinib possibly reduces plasma concentration of **levothyroxine**

Imidapril *see* ACE Inhibitors**Imipenem with Cilastatin**

- Antiepileptics: carbapenems reduce plasma concentration of **valproate**—avoid concomitant use
- Antivirals: increased risk of convulsions when imipenem with cilastatin given with **ganciclovir**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Imipramine *see* Antidepressants, Tricyclic**Immunoglobulins**

Note For advice on immunoglobulins and live virus vaccines, *see* under Normal Immunoglobulin, p. 628

Indacaterol *see* Sympathomimetics, Beta₂**Indapamide** *see* Diuretics**Indinavir**

Aldesleukin: plasma concentration of indinavir possibly increased by **aldesleukin**

- Anti-arrhythmics: indinavir possibly increases plasma concentration of **amiodarone**—avoid concomitant use; indinavir possibly increases plasma concentration of **flecainide** (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antibacterials: indinavir increases plasma concentration of **rifabutin** (also plasma concentration of indinavir reduced)—reduce rifabutin dose; metabolism of indinavir accelerated by **rifampicin** (reduced plasma concentration—avoid concomitant use); avoidance of concomitant indinavir in severe renal and hepatic impairment advised by manufacturer of **telithromycin**
- Anticoagulants: avoidance of indinavir advised by manufacturer of **apixaban** and **rivaroxaban**
- Antidepressants: plasma concentration of indinavir reduced by **St John's wort**—avoid concomitant use
- Antiepileptics: plasma concentration of indinavir possibly reduced by **carbamazepine** and **phenytoin**, also plasma concentration of carbamazepine and phenytoin possibly increased; plasma concentration of indinavir possibly reduced by **phenobarbital**
- Antifungals: plasma concentration of indinavir increased by **itraconazole** (consider reducing dose of indinavir)
- Antimalarials: caution with indinavir advised by manufacturer of **artemether with lumefantrine**; indinavir possibly increases plasma concentration of **quinine** (increased risk of toxicity)

Antimuscarinics: avoidance of indinavir advised by manufacturer of **darifenacin** and **tolterodine**; manufacturer of fesoterodine advises dose reduction when indinavir given with **fesoterodine**—consult fesoterodine product literature

- Antipsychotics: indinavir possibly increases plasma concentration of **aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); indinavir possibly increases plasma concentration of **pimozide** (increased risk of ventricular arrhythmias—avoid concomitant use); indinavir possibly increases plasma concentration of **quetiapine**—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: avoid concomitant use of indinavir with **atazanavir**; plasma concentration of both drugs increased when indinavir given with **darunavir**; absorption of indinavir reduced by **didanosine tablets** (give at least 1 hour apart); plasma concentration of indinavir reduced by **efavirenz** and **nevirapine**; plasma concentration of indinavir possibly reduced by **etravirine**—avoid concomitant use; indinavir increases plasma concentration of **maraviroc** (consider reducing dose of maraviroc); plasma

Indinavir• Antivirals (*continued*)

concentration of indinavir increased by **ritonavir**; indinavir increases plasma concentration of **saqueinavir**

- Anxiolytics and Hypnotics: increased risk of prolonged sedation when indinavir given with **alprazolam**—avoid concomitant use; indinavir possibly increases plasma concentration of **midazolam** (risk of prolonged sedation—avoid concomitant use of *oral* midazolam)

Atovaquone: plasma concentration of indinavir possibly reduced by **atovaquone**

Bosentan: plasma concentration of indinavir possibly reduced by **bosentan**

- Ciclosporin: indinavir increases plasma concentration of **ciclosporin**
- Colchicine: indinavir possibly increases risk of **colchicine** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)

Corticosteroids: plasma concentration of indinavir possibly reduced by **dexamethasone**

- Cytotoxics: indinavir possibly increases plasma concentration of **axitinib** (reduce dose of axitinib—consult axitinib product literature); indinavir possibly increases the plasma concentration of **bosutinib** and **cabazitaxel**—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; indinavir possibly increases plasma concentration of **crizotinib** and **everolimus**—manufacturer of crizotinib and everolimus advises avoid concomitant use; indinavir possibly increases plasma concentration of **pazopanib** (reduce dose of pazopanib); manufacturer of ruxotinib advises dose reduction when indinavir given with **ruxotinib**—consult ruxotinib product literature
- Ergot Alkaloids: increased risk of ergotism when indinavir given with **ergotamine**—avoid concomitant use
- 5HT₁-receptor Agonists: indinavir increases plasma concentration of **eletriptan** (risk of toxicity)—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when indinavir given with **atorvastatin**; possible increased risk of myopathy when indinavir given with **rosuvastatin**—manufacturer of rosuvastatin advises avoid concomitant use; increased risk of myopathy when indinavir given with **simvastatin** (avoid concomitant use); avoidance of indinavir advised by manufacturer of **lomitapide** (plasma concentration of lomitapide possibly increased)
- Orlistat: absorption of indinavir possibly reduced by **orlistat**
- Ranolazine: indinavir possibly increases plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: indinavir increases plasma concentration of **sildenafil**—reduce initial dose of sildenafil
- Tadalafil: indinavir possibly increases plasma concentration of **tadalafil**
- Vardenafil: indinavir increases plasma concentration of **vardenafil**—avoid concomitant use

Indometacin *see* NSAIDs**Indoramin** *see* Alpha-blockers**Infliximab**

- Abatacept: avoid concomitant use of infliximab with **abatacept**
- Anakinra: avoid concomitant use of infliximab with **anakinra**
- Vaccines: avoid concomitant use of infliximab with live **vaccines** (*see* p. 604)

Influenza Vaccine *see* Vaccines**Insulin** *see* Antidiabetics**Interferon Alfa** *see* Interferons

Interferon Gamma *see* Interferons**Interferons**

Note Peginterferon alfa interactions as for interferon alfa

- Antivirals: caution with peginterferon alfa advised by manufacturer of **adefovir**; increased risk of peripheral neuropathy when interferon alfa given with **telbivudine**
- Theophylline: interferon alfa inhibits metabolism of **theophylline** (consider reducing dose of theophylline)
- Vaccines: manufacturer of interferon gamma advises avoid concomitant use with **vaccines**

Ipilimumab

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Cytotoxics: manufacturer of ipilimumab advises avoid concomitant use with **vemurafenib**

Ipratropium *see* Antimuscarinics**Irbesartan** *see* Angiotensin-II Receptor Antagonists**Irinotecan**

- Antidepressants: metabolism of irinotecan accelerated by **St John's wort** (reduced plasma concentration—avoid concomitant use)
- Antiepileptics: plasma concentration of irinotecan and its active metabolite reduced by **carbamazepine**, **phenobarbital** and **phenytoin**
- Antifungals: increased risk of toxicity when irinotecan given with **itraconazole**—avoid concomitant use
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Antivirals: metabolism of irinotecan possibly inhibited by **atazanavir** (increased risk of toxicity)
- Cytotoxics: plasma concentration of active metabolite of irinotecan increased by **lapatinib**—consider reducing dose of irinotecan; plasma concentration of irinotecan increased by **regorafenib**; plasma concentration of irinotecan possibly increased by **sorafenib**

Iron

- Antacids: absorption of **oral** iron reduced by **oral magnesium salts** (as magnesium trisilicate)
- Antibacterials: **oral** iron reduces absorption of **ciprofloxacin**, **levofloxacin**, **moxifloxacin** and **ofloxacin**; **oral** iron reduces absorption of **norfloxacin** (give at least 2 hours apart); **oral** iron reduces absorption of **tetracyclines**, also absorption of **oral** iron reduced by tetracyclines
- Bisphosphonates: **oral** iron reduces absorption of **bisphosphonates**
- Calcium Salts: absorption of **oral** iron reduced by **calcium salts**
- Dopaminergics: **oral** iron reduces absorption of **entacapone**; **oral** iron possibly reduces absorption of **levodopa**
- Eltrombopag: **oral** iron possibly reduces absorption of **eltrombopag** (give at least 4 hours apart)
- Methyldopa: **oral** iron antagonises hypotensive effect of **methyldopa**
- Mycophenolate: **oral** iron reduces absorption of **mycophenolate**
- Penicillamine: **oral** iron reduces absorption of **penicillamine**
- Thyroid Hormones: **oral** iron reduces absorption of **levothyroxine** (give at least 2 hours apart)
- Trientine: absorption of **oral** iron reduced by **trientine**
- Zinc: **oral** iron reduces absorption of **zinc**, also absorption of **oral** iron reduced by zinc

Isocarboxazid *see* MAOIs**Isosflurane** *see* Anaesthetics, General**Isometheptene** *see* Sympathomimetics**Isoniazid**

- Anaesthetics, General: increased risk of hepatotoxicity when isoniazid given with **isoflurane**
- Analgesics: avoidance of isoniazid advised by manufacturer of **petidine**

Isoniazid (*continued*)

- Antacids: absorption of isoniazid reduced by **antacids**
- Antibacterials: increased risk of hepatotoxicity when isoniazid given with **rifampicin**; increased risk of CNS toxicity when isoniazid given with **cycloserine**
- Antiepileptics: isoniazid increases plasma concentration of **carbamazepine** (also possibly increased isoniazid hepatotoxicity); isoniazid inhibits metabolism of **ethosuximide** (increased plasma concentration and risk of toxicity); isoniazid possibly inhibits metabolism of **phenytoin** (increased risk of toxicity)
- Anxiolytics and Hypnotics: isoniazid inhibits the metabolism of **diazepam**
- Corticosteroids: plasma concentration of isoniazid possibly reduced by **corticosteroids**
- Disulfiram: isoniazid possibly increases CNS effects of **disulfiram**
- Dopaminergics: isoniazid possibly reduces effects of **levodopa**
- Theophylline: isoniazid possibly increases plasma concentration of **theophylline**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Isosorbide Dinitrate *see* Nitrates**Isosorbide Mononitrate** *see* Nitrates**Isotretinoin** *see* Retinoids**Itraconazole** *see* Antifungals, Triazole**Ivabradine**

- Anti-arrhythmics: increased risk of ventricular arrhythmias when ivabradine given with **amiodarone** or **disopyramide**
- Antibacterials: plasma concentration of ivabradine possibly increased by **clarithromycin** and **telithromycin**—avoid concomitant use; increased risk of ventricular arrhythmias when ivabradine given with **erythromycin**—avoid concomitant use
- Antidepressants: plasma concentration of ivabradine reduced by **St John's wort**—avoid concomitant use
- Antifungals: plasma concentration of ivabradine increased by **fluconazole**—reduce initial dose of ivabradine; plasma concentration of ivabradine possibly increased by **itraconazole**—avoid concomitant use
- Antimalarials: increased risk of ventricular arrhythmias when ivabradine given with **mefloquine**
- Antipsychotics: increased risk of ventricular arrhythmias when ivabradine given with **pimozide**
- Antivirals: plasma concentration of ivabradine possibly increased by **ritonavir**—avoid concomitant use
- Beta-blockers: increased risk of ventricular arrhythmias when ivabradine given with **sotalol**
- Calcium-channel Blockers: plasma concentration of ivabradine increased by **diltiazem** and **verapamil**—avoid concomitant use
- Grapefruit Juice: plasma concentration of ivabradine increased by **grapefruit juice**
- Pentamidine Isetionate: increased risk of ventricular arrhythmias when ivabradine given with **pentamidine isetionate**

Ivacaftor

- Antibacterials: plasma concentration of ivacaftor possibly increased by **clarithromycin**, **erythromycin** and **telithromycin** (see Dose under Ivacaftor, p. 165); plasma concentration of ivacaftor possibly reduced by **rifabutin**—manufacturer of ivacaftor advises avoid concomitant use; plasma concentration of ivacaftor reduced by **rifampicin**—manufacturer of ivacaftor advises avoid concomitant use
- Antidepressants: plasma concentration of ivacaftor possibly reduced by **St John's wort**—manufacturer of ivacaftor advises avoid concomitant use
- Antiepileptics: plasma concentration of ivacaftor possibly reduced by **carbamazepine**, **phenobarbital** and **phenytoin**—manufacturer of ivacaftor advises avoid concomitant use

Ivacaftor (*continued*)

- Antifungals: plasma concentration of ivacaftor increased by ●**fluconazole** (see Dose under Ivacaftor, p. 165); plasma concentration of ivacaftor possibly increased by ●**itraconazole**, ●**posaconazole** and ●**voriconazole** (see Dose under Ivacaftor, p. 165)
- Anxiolytics and Hypnotics: ivacaftor increases plasma concentration of **midazolam**
- Grapefruit Juice: plasma concentration of ivacaftor possibly increased by **grapefruit juice**—manufacturer of ivacaftor advises avoid concomitant use

Kaolin

- Analgesics: kaolin possibly reduces absorption of **aspirin**
- Antibacterials: kaolin possibly reduces absorption of **tetracyclines**
- Antimalarials: kaolin reduces absorption of **chloroquine** and **hydroxychloroquine**
- Antipsychotics: kaolin possibly reduces absorption of **phenothiazines**

Ketamine see Anaesthetics, General

Ketoprofen see NSAIDs

Ketorolac see NSAIDs

Ketotifen see Antihistamines

Labetalol see Beta-blockers

Lacidipine see Calcium-channel Blockers

Lacosamide

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and ●**tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by ●**SSRIs** and ●**tricyclics** (convulsive threshold lowered)
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by ●**mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ●**antipsychotics** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with ●**orlistat**

Lactulose

- Anticoagulants: lactulose possibly enhances anticoagulant effect of **coumarins**

Lamivudine

- Antibacterials: plasma concentration of lamivudine increased by **trimethoprim** (as co-trimoxazole)—avoid concomitant use of high-dose co-trimoxazole
- Antivirals: avoidance of lamivudine advised by manufacturer of **emtricitabine**
- Cytotoxics: manufacturer of lamivudine advises avoid concomitant use with ●**cladribine**
- Orlistat: absorption of lamivudine possibly reduced by ●**orlistat**

Lamotrigine

- Antibacterials: plasma concentration of lamotrigine reduced by ●**rifampicin**
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and ●**tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by ●**SSRIs** and ●**tricyclics** (convulsive threshold lowered)
- Antiepileptics: plasma concentration of lamotrigine often reduced by **carbamazepine**, also plasma concentration of an active metabolite of carbamazepine sometimes raised (but evidence is conflicting); plasma concentration of lamotrigine reduced by **phenobarbital** and **phenytoin**; plasma concentration of lamotrigine increased by ●**valproate** (increased risk of toxicity—reduce lamotrigine dose)
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by ●**mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ●**antipsychotics** (convulsive threshold lowered)

Lamotrigine (*continued*)

- Antivirals: plasma concentration of lamotrigine possibly reduced by **ritonavir**
- Oestrogens: plasma concentration of lamotrigine reduced by ●**oestrogens**—consider increasing dose of lamotrigine
- Orlistat: possible increased risk of convulsions when antiepileptics given with ●**orlistat**
- Progestogens: plasma concentration of lamotrigine possibly increased by **desogestrel**

Lanreotide

- Antidiabetics: lanreotide possibly reduces requirements for **antidiabetics**
- Ciclosporin: lanreotide reduces plasma concentration of **ciclosporin**

Lansoprazole see Proton Pump Inhibitors

Lanthanum

- Antibacterials: lanthanum possibly reduces absorption of **quinolones** (give at least 2 hours before or 4 hours after lanthanum)
- Antimalarials: lanthanum possibly reduces absorption of **chloroquine** and **hydroxychloroquine** (give at least 2 hours apart)
- Thyroid Hormones: lanthanum reduces absorption of **levothyroxine** (give at least 2 hours apart)

Lapatinib

- Antibacterials: manufacturer of lapatinib advises avoid concomitant use with ●**rifabutin**, ●**rifampicin** and ●**telithromycin**
 - Antidepressants: manufacturer of lapatinib advises avoid concomitant use with ●**St John's wort**
 - Antidiabetics: manufacturer of lapatinib advises avoid concomitant use with ●**repaglinide**
 - Antiepileptics: plasma concentration of lapatinib reduced by ●**carbamazepine**—avoid concomitant use; manufacturer of lapatinib advises avoid concomitant use with ●**phenytoin**
 - Antifungals: manufacturer of lapatinib advises avoid concomitant use with ●**itraconazole**, ●**posaconazole** and ●**voriconazole**
 - Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis); manufacturer of lapatinib advises avoid concomitant use with ●**pimozide**
 - Antivirals: avoidance of lapatinib advised by manufacturer of ●**boceprevir**; manufacturer of lapatinib advises avoid concomitant use with ●**ritonavir** and ●**sacquinavir**
 - Cytotoxics: lapatinib increases plasma concentration of **pazopanib**; possible increased risk of neutropenia when lapatinib given with **docetaxel**; increased risk of neutropenia when lapatinib given with ●**paclitaxel**; lapatinib increases plasma concentration of active metabolite of ●**irinotecan**—consider reducing dose of irinotecan
 - Grapefruit Juice: manufacturer of lapatinib advises avoid concomitant use with ●**grapefruit juice**
 - Ulcer-healing Drugs: absorption of lapatinib possibly reduced by **histamine H₂-antagonists** and **proton pump inhibitors**
- Laronidase**
- Antimalarials: effects of laronidase possibly inhibited by **chloroquine** and **hydroxychloroquine** (manufacturer of laronidase advises avoid concomitant use)
- Leflunomide**
- Note** Increased risk of toxicity with other haematotoxic and hepatotoxic drugs
- Antibacterials: plasma concentration of active metabolite of leflunomide possibly increased by **rifampicin**
 - Anticoagulants: leflunomide possibly enhances anticoagulant effect of **warfarin**
 - Antidiabetics: leflunomide possibly enhances hypoglycaemic effect of **tolbutamide**
 - Antiepileptics: leflunomide possibly increases plasma concentration of **phenytoin**

Leflunomide (*continued*)

- Cytotoxics: risk of toxicity when leflunomide given with **●methotrexate**
- Lipid-regulating Drugs: the effect of leflunomide is significantly decreased by **colestyramine** (enhanced elimination)—avoid unless drug elimination desired
- Vaccines: avoid concomitant use of leflunomide with live **●vaccines** (see p. 604)

Lenalidomide

- Antibacterials: plasma concentration of lenalidomide possibly increased by **●clarithromycin** (increased risk of toxicity)
- Antifungals: plasma concentration of lenalidomide possibly increased by **●itraconazole** (increased risk of toxicity)
- Calcium-channel Blockers: plasma concentration of lenalidomide possibly increased by **●verapamil** (increased risk of toxicity)
- Cardiac Glycosides: lenalidomide possibly increases plasma concentration of **digoxin**
- Ciclosporin: plasma concentration of lenalidomide possibly increased by **●ciclosporin** (increased risk of toxicity)

Lercanidipine *see* Calcium-channel Blockers

Leukotriene Receptor Antagonists

- Analgesics: plasma concentration of zafirlukast increased by **aspirin**
- Antibacterials: plasma concentration of zafirlukast reduced by **erythromycin**
- Anticoagulants: zafirlukast enhances anticoagulant effect of **warfarin**
- Antiepileptics: plasma concentration of montelukast reduced by **phenobarbital**
- Antifungals: plasma concentration of zafirlukast increased by **fluconazole**
- Lipid-regulating Drugs: plasma concentration of montelukast increased by **gemfibrozil**
- Theophylline: zafirlukast possibly increases plasma concentration of **theophylline**, also plasma concentration of zafirlukast reduced

Levamisole

- Alcohol: possibility of disulfiram-like reaction when levamisole given with **alcohol**
- Anticoagulants: levamisole possibly enhances anticoagulant effect of **●warfarin**
- Antiepileptics: levamisole possibly increases plasma concentration of **phenytoin**

Levetiracetam

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **●tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **●SSRIs** and **●tricyclics** (convulsive threshold lowered)
- Antiepileptics: levetiracetam possibly increases risk of **carbamazepine** toxicity
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by **●mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **●antipsychotics** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with **●orlistat**

Levobunolol *see* Beta-blockers

Levobupivacaine

- Anti-arrhythmics: increased myocardial depression when levobupivacaine given with **anti-arrhythmics**

Levocarnitine

- Anticoagulants: levocarnitine possibly enhances anticoagulant effect of **coumarins**

Levocetirizine *see* Antihistamines

Levodopa

- ACE Inhibitors: enhanced hypotensive effect when levodopa given with **ACE inhibitors**

Levodopa (*continued*)

- Adrenergic Neurone Blockers: enhanced hypotensive effect when levodopa given with **adrenergic neurone blockers**
- Alpha-blockers: enhanced hypotensive effect when levodopa given with **alpha-blockers**
- Anaesthetics, General: increased risk of arrhythmias when levodopa given with **●volatile liquid general anaesthetics**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when levodopa given with **angiotensin-II receptor antagonists**
- Antibacterials: effects of levodopa possibly reduced by **isoniazid**
- Antidepressants: risk of hypertensive crisis when levodopa given with **●MAOIs**, avoid levodopa for at least 2 weeks after stopping MAOIs; increased risk of side-effects when levodopa given with **moclobemide**
- Antiepileptics: effects of levodopa possibly reduced by **phenytoin**
- Antimuscarinics: absorption of levodopa possibly reduced by **antimuscarinics**
- Antipsychotics: effects of levodopa antagonised by **antipsychotics**; avoidance of levodopa advised by manufacturer of **amisulpride** (antagonism of effect)
- Anxiolytics and Hypnotics: effects of levodopa possibly antagonised by **benzodiazepines**
- Beta-blockers: enhanced hypotensive effect when levodopa given with **beta-blockers**
- Bupropion: increased risk of side-effects when levodopa given with **bupropion**
- Calcium-channel Blockers: enhanced hypotensive effect when levodopa given with **calcium-channel blockers**
- Clonidine: enhanced hypotensive effect when levodopa given with **clonidine**
- Diazoxide: enhanced hypotensive effect when levodopa given with **diazoxide**
- Diuretics: enhanced hypotensive effect when levodopa given with **diuretics**
- Dopaminergics: enhanced effects and increased toxicity of levodopa when given with **selegiline** (reduce dose of levodopa)
- Iron: absorption of levodopa possibly reduced by **oral iron**
- Memantine: effects of dopaminergics possibly enhanced by **memantine**
- Methyldopa: enhanced hypotensive effect when levodopa given with **methyldopa**; antiparkinsonian effect of dopaminergics antagonised by **methyldopa**
- Moxonidine: enhanced hypotensive effect when levodopa given with **moxonidine**
- Muscle Relaxants: possible agitation, confusion and hallucinations when levodopa given with **baclofen**
- Nitrates: enhanced hypotensive effect when levodopa given with **nitrates**
- Vasodilator Antihypertensives: enhanced hypotensive effect when levodopa given with **hydralazine**, **minoxidil** or **sodium nitroprusside**
- Vitamins: effects of levodopa reduced by **pyridoxine** when given without dopa-decarboxylase inhibitor

Levofloxacin *see* Quinolones

Levofolinic Acid *see* Folate

Levomepromazine *see* Antipsychotics

Levonorgestrel *see* Progestogens

Levothyroxine *see* Thyroid Hormones

Lidocaine

- Note** Interactions less likely when lidocaine used topically
- Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with **bupivacaine**, **levobupivacaine**, **prilocaine** or **ropivacaine**
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other **●anti-arrhythmics**

Lidocaine (*continued*)

- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with ●**antipsychotics** that prolong the QT interval
- Antivirals: plasma concentration of lidocaine possibly increased by ●**atazanavir** and ●**lopinavir**; plasma concentration of lidocaine possibly increased by ●**darunavir** and ●**fosamprenavir**—avoid concomitant use; increased risk of ventricular arrhythmias when lidocaine given with ●**saquinavir**—avoid concomitant use; caution with *intravenous* lidocaine advised by manufacturer of **telaprevir**
- Beta-blockers: increased myocardial depression when anti-arrhythmics given with ●**beta-blockers**; possible increased risk of lidocaine toxicity when given with ●**nadolol**; increased risk of lidocaine toxicity when given with ●**propranolol**
- Diuretics: action of lidocaine antagonised by hypokalaemia caused by ●**acetazolamide**, ●**loop diuretics** or ●**thiazides and related diuretics**
- Muscle Relaxants: neuromuscular blockade enhanced and prolonged when lidocaine given with ●**suxamethonium**
- Ulcer-healing Drugs: plasma concentration of lidocaine increased by ●**cimetidine** (increased risk of toxicity)

Linagliptin *see* Antidiabetics

Linezolid

Note Linezolid is a reversible, non-selective MAO inhibitor—see interactions of MAOIs

Antibacterials: plasma concentration of linezolid reduced by ●**rifampicin** (possible therapeutic failure of linezolid)

Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Liothyronine *see* Thyroid Hormones

Lipid-regulating Drugs *see* Colesevelam, Colestipol, Colestyramine, Ezetimibe, Fibrates, Lomitapide, Nicotinic Acid, and Statins

Liraglutide *see* Antidiabetics

Lisdexamfetamine *see* Sympathomimetics

Lisinopril *see* ACE Inhibitors

Lithium

- ACE Inhibitors: excretion of lithium reduced by ●**ACE inhibitors** (increased plasma concentration)
- Analgesics: excretion of lithium reduced by ●**NSAIDs** (increased risk of toxicity); excretion of lithium reduced by ●**ketorolac** (increased risk of toxicity)—avoid concomitant use
- Angiotensin-II Receptor Antagonists: excretion of lithium reduced by ●**angiotensin-II receptor antagonists** (increased plasma concentration)
- Antacids: excretion of lithium increased by ●**sodium bicarbonate** (reduced plasma concentration)
- Anti-arrhythmics: avoidance of lithium advised by manufacturer of ●**amiodarone** (risk of ventricular arrhythmias)
- Antibacterials: increased risk of lithium toxicity when given with ●**metronidazole**
- Antidepressants: possible increased serotonergic effects when lithium given with ●**venlafaxine**; increased risk of CNS effects when lithium given with ●**SSRIs** (lithium toxicity reported); risk of toxicity when lithium given with ●**tricyclics**
- Antiepileptics: neurotoxicity may occur when lithium given with ●**carbamazepine** or ●**phenytoin** without increased plasma concentration of lithium; plasma concentration of lithium possibly affected by ●**topiramate**
- Antipsychotics: increased risk of extrapyramidal side-effects and possibly neurotoxicity when lithium given with ●**clozapine**, ●**flupentixol**, ●**haloperidol**, ●**phenothiazines**, ●**risperidone** or ●**zuclopentixol**; possible risk of toxicity when lithium given with ●**olanza-**

Lithium

● Antipsychotics (*continued*)

●**pine**; increased risk of extrapyramidal side-effects when lithium given with ●**sulpiride**

Anxiolytics and Hypnotics: increased risk of neurotoxicity when lithium given with ●**clonazepam**

Calcium-channel Blockers: neurotoxicity may occur when lithium given with ●**diltiazem** or ●**verapamil** without increased plasma concentration of lithium

● Cytotoxics: increased risk of ventricular arrhythmias when lithium given with ●**arsenic trioxide**

● Dapoxetine: possible increased risk of serotonergic effects when lithium given with ●**dapoxetine** (manufacturer of dapoxetine advises lithium should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping lithium)

● Diuretics: excretion of lithium increased by ●**acetazolamide**; excretion of lithium reduced by ●**loop diuretics** and ●**thiazides and related diuretics** (increased plasma concentration and risk of toxicity)—loop diuretics safer than thiazides; excretion of lithium reduced by ●**potassium-sparing diuretics and aldosterone antagonists** (increased plasma concentration and risk of toxicity)

5HT₁-receptor Agonists: possible risk of toxicity when lithium given with ●**sumatriptan**

● Methyldopa: neurotoxicity may occur when lithium given with ●**methyldopa** without increased plasma concentration of lithium

Muscle Relaxants: lithium enhances effects of ●**muscle relaxants**; hyperkinesia caused by lithium possibly aggravated by ●**baclofen**

Parasympathomimetics: lithium antagonises effects of ●**neostigmine**

Theophylline: excretion of lithium increased by ●**theophylline** (reduced plasma concentration)

Lixisenatide *see* Antidiabetics

Lofepamine *see* Antidepressants, Tricyclic

Lofexidine

Alcohol: increased sedative effect when lofexidine given with ●**alcohol**

Anxiolytics and Hypnotics: increased sedative effect when lofexidine given with ●**anxiolytics and hypnotics**

Lomitapide

Alcohol: manufacturer of lomitapide advises avoid concomitant use with ●**alcohol**

● Anti-arrhythmics: manufacturer of lomitapide advises avoid concomitant use with ●**dronedarone** (plasma concentration of lomitapide possibly increased)

● Antibacterials: manufacturer of lomitapide advises avoid concomitant use with ●**clarithromycin**, ●**erythromycin** and ●**telithromycin** (plasma concentration of lomitapide possibly increased)

Anticoagulants: lomitapide possibly enhances anticoagulant effect of ●**warfarin**

● Antifungals: manufacturer of lomitapide advises avoid concomitant use with ●**triazoles** (plasma concentration of lomitapide possibly increased)

● Antivirals: manufacturer of lomitapide advises avoid concomitant use with ●**darunavir**, ●**fosamprenavir**, ●**indinavir**, ●**lopinavir**, ●**ritonavir**, ●**saquinavir**, ●**telaprevir** and ●**tipranavir** (plasma concentration of lomitapide possibly increased)

Aprepitant: manufacturer of lomitapide advises dose reduction when lomitapide given with ●**fosaprepitant** (see Dose under Lomitapide, BNF section 2.12)

● Calcium-channel Blockers: manufacturer of lomitapide advises avoid concomitant use with ●**diltiazem** and ●**verapamil** (plasma concentration of lomitapide possibly increased)

Grapefruit Juice: manufacturer of lomitapide advises avoid concomitant use with ●**grapefruit juice**

● Lipid-regulating Drugs: lomitapide increases plasma concentration of ●**atorvastatin**; lomitapide increases plasma concentration of ●**simvastatin** (see Dose

Lomitapide

- **Lipid-regulating Drugs** (*continued*)
under Simvastatin, BNF section 2.12); absorption of lomitapide possibly reduced by **bile acid sequestrants** (give at least 4 hours apart)
- Ranolazine: manufacturer of lomitapide advises dose reduction when lomitapide given with **ranolazine** (see Dose under Lomitapide, BNF section 2.12)
- Ulcer-healing Drugs: manufacturer of lomitapide advises dose reduction when lomitapide given with **cimetidine** (see Dose under Lomitapide, BNF section 2.12)

Lomustine

- **Antipsychotics**: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Ulcer-healing Drugs: myelosuppressive effects of lomustine possibly enhanced by **cimetidine**

Loperamide

Desmopressin: loperamide increases plasma concentration of **oral desmopressin**

Lopinavir

Note In combination with ritonavir as **Kaletra**® (ritonavir is present to inhibit lopinavir metabolism and increase plasma lopinavir concentration)—see also Ritonavir

- **Anti-arrhythmics**: lopinavir possibly increases plasma concentration of **flecainide** (increased risk of ventricular arrhythmias—avoid concomitant use); lopinavir possibly increases plasma concentration of **lidocaine**
- **Antibacterials**: plasma concentration of lopinavir reduced by **rifampicin**—avoid concomitant use; avoidance of concomitant lopinavir in severe renal and hepatic impairment advised by manufacturer of **telithromycin**
- Anticoagulants: avoidance of lopinavir advised by manufacturer of **apixaban**; manufacturers advise avoid concomitant use of lopinavir with **rivaroxaban**
- **Antidepressants**: plasma concentration of lopinavir reduced by **St John's wort**—avoid concomitant use
- **Antiepileptics**: plasma concentration of lopinavir possibly reduced by **carbamazepine**, **phenobarbital** and **phenytoin**
- Antihistamines: lopinavir possibly increases plasma concentration of **chlorphenamine**
- Antimalarials: caution with lopinavir advised by manufacturer of **artemether with lumefantrine**
- Antimuscarinics: avoidance of lopinavir advised by manufacturer of **darifenacin** and **tolterodine**
- **Antipsychotics**: lopinavir possibly increases plasma concentration of **aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); lopinavir possibly increases plasma concentration of **quetiapine**—manufacturer of quetiapine advises avoid concomitant use
- **Antivirals**: manufacturers advise avoid concomitant use of lopinavir with **boceprevir** and **telaprevir**; lopinavir reduces plasma concentration of **darunavir**, also plasma concentration of lopinavir increased (avoid concomitant use); plasma concentration of lopinavir reduced by **efavirenz**—consider increasing dose of lopinavir; lopinavir boosted with ritonavir increases plasma concentration of **elvitegravir** (reduce dose of elvitegravir); lopinavir reduces plasma concentration of **fosamprenavir**, effect on lopinavir plasma concentration not predictable—avoid concomitant use; lopinavir increases plasma concentration of **maraviroc** (consider reducing dose of maraviroc); plasma concentration of lopinavir possibly reduced by **nevirapine**—consider increasing dose of lopinavir; increased risk of ventricular arrhythmias when lopinavir given with **saquinavir**—avoid concomitant use; lopinavir increases plasma concentration of **tenofovir**; plasma concentration of lopinavir reduced by **tipranavir**

Lopinavir (*continued*)

- **Bosentan**: lopinavir increases plasma concentration of **bosentan** (consider reducing dose of bosentan)
- Corticosteroids**: plasma concentration of lopinavir possibly reduced by **dexamethasone**
- **Cytotoxics**: manufacturer of ruxolitinib advises dose reduction when lopinavir given with **ruxolitinib**—consult ruxolitinib product literature
- Eltrombopag**: lopinavir possibly reduces plasma concentration of **eltrombopag**
- **Lipid-regulating Drugs**: possible increased risk of myopathy when lopinavir given with **atorvastatin**; possible increased risk of myopathy when lopinavir given with **rosuvastatin**—manufacturer of rosuvastatin advises avoid concomitant use; possible increased risk of myopathy when lopinavir given with **simvastatin**—avoid concomitant use; avoidance of lopinavir advised by manufacturer of **lomitapide** (plasma concentration of lomitapide possibly increased)
- **Orlistat**: absorption of lopinavir possibly reduced by **orlistat**
- **Ranolazine**: lopinavir possibly increases plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use
- Sirolimus**: lopinavir possibly increases plasma concentration of **sirolimus**
- Sympathomimetics**, β_2 : manufacturer of lopinavir advises avoid concomitant use with **salmeterol**

Loprazolam see Anxiolytics and Hypnotics

Loratadine see Antihistamines

Lorazepam see Anxiolytics and Hypnotics

Lormetazepam see Anxiolytics and Hypnotics

Losartan see Angiotensin-II Receptor Antagonists

Lumefantrine see Artemether with Lumefantrine

Lymecycline see Tetracyclines

Macitentan

- **Antibacterials**: plasma concentration of macitentan reduced by **rifampicin**—avoid concomitant use
- Antidepressants**: manufacturer of macitentan advises avoid concomitant use with **St John's wort**
- Antiepileptics**: manufacturer of macitentan advises avoid concomitant use with **carbamazepine** and **phenytoin**

Macrolides

Note See also Telithromycin

Note Interactions do not apply to small amounts of erythromycin used topically

Analgesics: erythromycin increases plasma concentration of **alfentanil**; clarithromycin possibly increases plasma concentration of **fentanyl**

Antacids: absorption of azithromycin reduced by **antacids**

- **Anti-arrhythmics**: increased risk of ventricular arrhythmias when **parenteral** erythromycin given with **amiodarone**—avoid concomitant use; erythromycin increases plasma concentration of **disopyramide** (increased risk of toxicity); clarithromycin possibly increases plasma concentration of **disopyramide** (increased risk of ventricular arrhythmias); azithromycin possibly increases plasma concentration of **disopyramide** (increased risk of toxicity); erythromycin increases plasma concentration of **dronedrone** (increased risk of ventricular arrhythmias—avoid concomitant use); avoidance of clarithromycin advised by manufacturer of **dronedrone** (risk of ventricular arrhythmias)
- **Antibacterials**: increased risk of ventricular arrhythmias when **parenteral** erythromycin given with **moxifloxacin**—avoid concomitant use; increased risk of side-effects including neutropenia when azithromycin given with **rifabutin**; clarithromycin increases plasma concentration of **rifabutin** (increased risk of toxicity—reduce rifabutin dose); erythromycin possibly increases plasma concentration of **rifabutin** (increased risk of toxicity—reduce

Macrolides

- **Antibacterials** (*continued*)
rifabutin dose); plasma concentration of clarithromycin reduced by **rifamycins**
- **Anticoagulants**: azithromycin possibly enhances anticoagulant effect of ●**coumarins**; clarithromycin and erythromycin enhance anticoagulant effect of ●**coumarins**; possible increased risk of bleeding when clarithromycin given with **dabigatran**
- **Antidepressants**: avoidance of macrolides advised by manufacturer of ●**reboxetine**; avoidance of *intravenous* erythromycin advised by manufacturer of ●**citalopram** and ●**escitalopram** (risk of ventricular arrhythmias); clarithromycin possibly increases plasma concentration of **trazodone**
- Antidiabetics: clarithromycin enhances effects of **repaglinide**
- **Antiepileptics**: clarithromycin increases plasma concentration of ●**carbamazepine** (consider reducing dose of carbamazepine); erythromycin increases plasma concentration of ●**carbamazepine**; clarithromycin inhibits metabolism of **phenytoin** (increased plasma concentration); erythromycin possibly inhibits metabolism of **valproate** (increased plasma concentration)
- Antifungals: avoidance of erythromycin advised by manufacturer of **fluconazole**; clarithromycin increases plasma concentration of **itraconazole**
- **Antihistamines**: manufacturer of loratadine advises erythromycin possibly increases plasma concentration of **loratadine**; macrolides possibly inhibit metabolism of ●**mizolastine** (avoid concomitant use); erythromycin inhibits metabolism of ●**mizolastine**—avoid concomitant use; erythromycin increases plasma concentration of **rupatadine**
- **Antimalarials**: avoidance of macrolides advised by manufacturer of ●**piperaquine** with **artemimol** (possible risk of ventricular arrhythmias); avoidance of macrolides advised by manufacturer of ●**artemether** with **lumefantrine**
- Antimuscarinics: erythromycin possibly increases plasma concentration of **darifenacin**; manufacturer of fesoterodine advises dose reduction when clarithromycin given with **fesoterodine**—consult fesoterodine product literature; avoidance of clarithromycin and erythromycin advised by manufacturer of **tolterodine**
- **Antipsychotics**: avoidance of macrolides advised by manufacturer of ●**droperidol** (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when *parenteral* erythromycin given with ●**zuclopenthixol**—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with ●**amisulpride**—avoid concomitant use; erythromycin possibly increases plasma concentration of ●**clozapine** (possible increased risk of convulsions); possible increased risk of ventricular arrhythmias when erythromycin given with ●**pimozide**—avoid concomitant use; increased risk of ventricular arrhythmias when clarithromycin given with ●**pimozide**—avoid concomitant use; erythromycin increases plasma concentration of ●**quetiapine**—manufacturer of quetiapine advises avoid concomitant use; clarithromycin possibly increases plasma concentration of ●**quetiapine**—manufacturer of quetiapine advises avoid concomitant use; increased risk of ventricular arrhythmias when *parenteral* erythromycin given with ●**sulpiride**
- **Antivirals**: plasma concentration of both drugs increased when clarithromycin given with **atazanavir**; plasma concentration of clarithromycin reduced by **efavirenz**, also plasma concentration of active metabolite of clarithromycin increased; plasma concentration of clarithromycin reduced by ●**etravirine** and **nevirapine** (but concentration of an active metabolite increased), also plasma concentration of

Macrolides

- **Antivirals** (*continued*)
etravirine and nevirapine increased; clarithromycin possibly increases plasma concentration of ●**maraviroc** (consider reducing dose of maraviroc); avoidance of clarithromycin and erythromycin advised by manufacturer of ●**rilpivirine** (plasma concentration of rilpivirine possibly increased); plasma concentration of azithromycin and erythromycin possibly increased by **ritonavir**; plasma concentration of clarithromycin increased by ●**ritonavir** (reduce dose of clarithromycin in renal impairment); plasma concentration of both drugs possibly increased when clarithromycin given with ●**sacquinavir** and ●**telaprevir** (increased risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when erythromycin given with ●**sacquinavir**—avoid concomitant use; plasma concentration of both drugs possibly increased when erythromycin given with ●**telaprevir** (increased risk of ventricular arrhythmias); plasma concentration of clarithromycin increased by ●**tipranavir** (reduce dose of clarithromycin in renal impairment), also clarithromycin increases plasma concentration of tipranavir; clarithromycin tablets reduce absorption of **zidovudine** (give at least 2 hours apart)
- **Anxiolytics and Hypnotics**: clarithromycin and erythromycin inhibit metabolism of ●**midazolam** (increased plasma concentration with increased sedation); erythromycin increases plasma concentration of **buspirone** (reduce dose of buspirone); erythromycin inhibits the metabolism of **zopiclone**
- **Appetitant**: clarithromycin possibly increases plasma concentration of **aprepitant**
- **Atomoxetine**: increased risk of ventricular arrhythmias when *parenteral* erythromycin given with ●**atomoxetine**
- **Calcium-channel Blockers**: clarithromycin and erythromycin possibly inhibit metabolism of ●**calcium-channel blockers** (increased risk of side-effects); avoidance of erythromycin advised by manufacturer of **lercanidipine**
- Cardiac Glycosides: macrolides increase plasma concentration of **digoxin** (increased risk of toxicity)
- **Ciclosporin**: macrolides possibly inhibit metabolism of ●**ciclosporin** (increased plasma concentration); clarithromycin and erythromycin inhibit metabolism of ●**ciclosporin** (increased plasma concentration)
- **Cilostazol**: clarithromycin possibly increases plasma concentration of ●**cilostazol** (see Dose under Cilostazol, BNF section 2.6.4); erythromycin increases plasma concentrations of ●**cilostazol** (see Dose under Cilostazol, BNF section 2.6.4)
- **Clopidogrel**: erythromycin possibly reduces antiplatelet effect of ●**clopidogrel**
- **Colchicine**: azithromycin, clarithromycin and erythromycin possibly increase risk of ●**colchicine** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: erythromycin possibly inhibits metabolism of **corticosteroids**; clarithromycin possibly increases plasma concentration of **methylprednisolone**; erythromycin inhibits the metabolism of **methylprednisolone**
- **Cytotoxics**: erythromycin possibly increases the plasma concentration of **afatinib**—manufacturer of afatinib advises separating administration of erythromycin by 6 to 12 hours; clarithromycin and erythromycin possibly increase plasma concentration of **axitinib** (reduce dose of axitinib—consult axitinib product literature); clarithromycin and erythromycin possibly increase the plasma concentration of ●**bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; clarithromycin possibly increases plasma concentration of ●**crizotinib** and ●**everolimus**—manu-

Macrolides● Cytotoxics (*continued*)

facturer of crizotinib and everolimus advises avoid concomitant use; erythromycin increases plasma concentration of ●**everolimus** (consider reducing the dose of everolimus—consult everolimus product literature); avoidance of clarithromycin advised by manufacturer of ●**nilotinib**; clarithromycin possibly increases plasma concentration of ●**pazopanib** (reduce dose of pazopanib); manufacturer of ruxolitinib advises dose reduction when clarithromycin given with ●**ruxolitinib**—consult ruxolitinib product literature; possible increased risk of ventricular arrhythmias when *parenteral* erythromycin given with ●**vandetanib**—avoid concomitant use; clarithromycin possibly increases the plasma concentration of ●**cabazitaxel**—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel; *in vitro* studies suggest a possible interaction between erythromycin and **docetaxel** (consult docetaxel product literature); increased risk of ventricular arrhythmias when erythromycin given with ●**arsenic trioxide**; erythromycin increases toxicity of ●**vinblastine**—avoid concomitant use; possible increased risk of neutropenia when clarithromycin given with ●**vinorelbine**

Dapoxetine: manufacturer of dapoxetine advises dose reduction when clarithromycin and erythromycin given with **dapoxetine** (see Dose under Dapoxetine, BNF section 7.4.6)

● Diuretics: clarithromycin increases plasma concentration of ●**eplerenone**—avoid concomitant use; erythromycin increases plasma concentration of **eplerenone** (reduce dose of eplerenone)● Domperidone: erythromycin increases plasma concentration of ●**domperidone**—possible increased risk of ventricular arrhythmias

Dopaminergics: erythromycin increases plasma concentration of **bromocriptine** and **cabergoline** (increased risk of toxicity); macrolides possibly increase plasma concentration of **bromocriptine** and **cabergoline** (increased risk of toxicity)

● Ergot Alkaloids: increased risk of ergotism when macrolides given with ●**ergotamine**—avoid concomitant use

Fidaxomicin: avoidance of clarithromycin and erythromycin advised by manufacturer of **fidaxomicin**

● 5HT₁-receptor Agonists: clarithromycin and erythromycin increase plasma concentration of ●**eletriptan** (risk of toxicity)—avoid concomitant use● Ivabradine: clarithromycin possibly increases plasma concentration of ●**ivabradine**—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with ●**ivabradine**—avoid concomitant use● Ivacaftor: clarithromycin and erythromycin possibly increase plasma concentration of ●**ivacaftor** (see Dose under Ivacaftor, p. 165)● Lenalidomide: clarithromycin possibly increases plasma concentration of ●**lenalidomide** (increased risk of toxicity)

Leukotriene Receptor Antagonists: erythromycin reduces plasma concentration of **zafirlukast**

● Lipid-regulating Drugs: clarithromycin increases plasma concentration of ●**atorvastatin** and **pravastatin**; possible increased risk of myopathy when erythromycin given with **atorvastatin**; erythromycin increases plasma concentration of **pravastatin**; erythromycin reduces plasma concentration of **rosuvastatin**; increased risk of myopathy when clarithromycin or erythromycin given with ●**simvastatin** (avoid concomitant use); avoidance of clarithromycin and erythromycin advised by manufacturer of ●**lomitapide** (plasma concentration of lomitapide possibly increased)**Macrolides (*continued*)**

Mirabegron: when given with clarithromycin avoid or reduce dose of **mirabegron** in hepatic or renal impairment—see Mirabegron, BNF section 7.4.2

Oestrogens: erythromycin increases plasma concentration of **estradiol**

Parasympathomimetics: erythromycin increases plasma concentration of **galantamine**

● Pentamidine Isetionate: increased risk of ventricular arrhythmias when *parenteral* erythromycin given with ●**pentamidine isetionate**

Progestogens: erythromycin increases plasma concentration of **dienogest**

● Ranolazine: clarithromycin possibly increases plasma concentration of ●**ranolazine**—manufacturer of ranolazine advises avoid concomitant use● Sildenafil: clarithromycin increases plasma concentration of ●**sildenafil** (consider reducing dose of sildenafil); erythromycin increases plasma concentration of **sildenafil**—reduce initial dose of sildenafil● Sirolimus: clarithromycin increases plasma concentration of ●**sirolimus**—avoid concomitant use; plasma concentration of both drugs increased when erythromycin given with ●**sirolimus**● Tacrolimus: clarithromycin and erythromycin increase plasma concentration of ●**tacrolimus**

Tadalafil: clarithromycin and erythromycin possibly increase plasma concentration of **tadalafil**

● Theophylline: clarithromycin possibly increases plasma concentration of **theophylline**; erythromycin increases plasma concentration of ●**theophylline** (also theophylline may reduce absorption of *oral* erythromycin)● Ticagrelor: clarithromycin possibly increases plasma concentration of ●**ticagrelor**—manufacturer of ticagrelor advises avoid concomitant use; erythromycin possibly increases plasma concentration of **ticagrelor**

Ulcer-healing Drugs: plasma concentration of erythromycin increased by **cimetidine** (increased risk of toxicity, including deafness); plasma concentration of both drugs increased when clarithromycin given with **omeprazole**

Ulipristal: avoidance of clarithromycin advised by manufacturer of **ulipristal**; erythromycin increases plasma concentration of **ulipristal**—manufacturer of ulipristal advises avoid concomitant use

Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Vardenafil: clarithromycin possibly increases plasma concentration of **vardenafil** (consider reducing initial dose of vardenafil); erythromycin increases plasma concentration of **vardenafil** (reduce dose of vardenafil)

Magnesium (parenteral)● Calcium-channel Blockers: profound hypotension reported with concomitant use of parenteral magnesium and ●**nifedipine** in pre-eclampsia
Muscle Relaxants: parenteral magnesium enhances effects of **non-depolarising muscle relaxants** and **suxamethonium****Magnesium Salts (oral)** *see* Antacids**Mannitol**

Antibacterials: avoidance of mannitol advised by manufacturer of **tobramycin**

Ciclosporin: possible increased risk of nephrotoxicity when mannitol given with **ciclosporin**

MAOIs

Note For interactions of reversible MAO-A inhibitors (RIMAs) see Moclobemide, and for interactions of MAO-B inhibitors see Rasagiline and Selegiline; the antibacterial Linezolid is a reversible, non-selective MAO inhibitor

ACE Inhibitors: MAOIs possibly enhance hypotensive effect of **ACE inhibitors**

MAOIs (continued)

Adrenergic Neurons Blockers: enhanced hypotensive effect when MAOIs given with **adrenergic neurone blockers**

- Alcohol: MAOIs interact with tyramine found in some beverages containing **alcohol** and some dealcoholised beverages (hypertensive crisis)—if no tyramine, enhanced hypotensive effect

Alpha₂-adrenoceptor Stimulants: avoidance of MAOIs advised by manufacturer of **apraclonidine** and **bri-mondine**

- Alpha-blockers: avoidance of MAOIs advised by manufacturer of **indoramin**; enhanced hypotensive effect when MAOIs given with **alpha-blockers**
- Analgesics: possible increased serotonergic effects when MAOIs given with **fentanyl**; CNS excitation or depression (hypertension or hypotension) when MAOIs given with **pethidine**—avoid concomitant use and for 2 weeks after stopping MAOIs; possible increased serotonergic effects and increased risk of convulsions when MAOIs given with **tramadol**—some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs; avoidance of MAOIs advised by manufacturer of **nefopam**; possible CNS excitation or depression (hypertension or hypotension) when MAOIs given with **opioid analgesics**—some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs

Angiotensin-II Receptor Antagonists: MAOIs possibly enhance hypotensive effect of **angiotensin-II receptor antagonists**

- Antidepressants: increased risk of hypertension and CNS excitation when MAOIs given with **reboxetine** (MAOIs should not be started until 1 week after stopping reboxetine, avoid reboxetine for 2 weeks after stopping MAOIs); after stopping MAOIs do not start **citalopram**, **escitalopram**, **fluvoxamine**, **paroxetine** or **sertraline** for 2 weeks, also MAOIs should not be started until at least 1 week after stopping citalopram, escitalopram, fluvoxamine, paroxetine or sertraline; after stopping MAOIs do not start **fluoxetine** for 2 weeks, also MAOIs should not be started until at least 5 weeks after stopping fluoxetine; after stopping MAOIs do not start **duloxetine** for 2 weeks, also MAOIs should not be started until at least 5 days after stopping duloxetine; enhanced CNS effects and toxicity when MAOIs given with **venlafaxine** (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping venlafaxine); increased risk of hypertension and CNS excitation when MAOIs given with other **MAOIs** (avoid for at least 2 weeks after stopping previous MAOIs and then start at a reduced dose); after stopping MAOIs do not start **moclobemide** for at least 1 week; MAOIs increase CNS effects of **SSRIs** (risk of serious toxicity); after stopping MAOIs do not start **mirtazapine** for 2 weeks, also MAOIs should not be started until at least 2 weeks after stopping mirtazapine; after stopping MAOIs do not start **tricyclic-related antidepressants** for 2 weeks, also MAOIs should not be started until at least 1–2 weeks after stopping tricyclic-related antidepressants; increased risk of hypertension and CNS excitation when MAOIs given with **tricyclics**, tricyclics should not be started until 2 weeks after stopping MAOIs (3 weeks if starting clomipramine or imipramine), also MAOIs should not be started for at least 1–2 weeks after stopping tricyclics (3 weeks in the case of clomipramine or imipramine)

Antidiabetics: MAOIs possibly enhance hypoglycaemic effect of **antidiabetics**; MAOIs enhance hypoglycaemic effect of **insulin**, **metformin** and **sulfonylureas**

MAOIs (continued)

- Antiepileptics: MAOIs possibly antagonise anti-convulsant effect of **antiepileptics** (convulsive threshold lowered); avoidance for 2 weeks after stopping MAOIs advised by manufacturer of **carbamazepine**, also antagonism of anticonvulsant effect

Antihistamines: avoidance of MAOIs advised by manufacturer of **hydroxyzine**; avoidance of promethazine for 2 weeks after stopping MAOIs advised by manufacturer of **promethazine**; increased antimuscarinic and sedative effects when MAOIs given with **antihistamines**

- Antimalarials: avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperaquine with arteminol**
- Antimuscarinics: increased risk of antimuscarinic side-effects when MAOIs given with **antimuscarinics**
- Antipsychotics: CNS effects of MAOIs possibly increased by **clozapine**
- Anxiolytics and Hypnotics: avoidance of MAOIs advised by manufacturer of **buspirone**; manufacturer of **tranylcypromine** advises avoid **buspirone** for 14 days after stopping tranylcypromine
- Atomoxetine: after stopping MAOIs do not start **atomoxetine** for 2 weeks, also MAOIs should not be started until at least 2 weeks after stopping atomoxetine; possible increased risk of convulsions when antidepressants given with **atomoxetine**
- Beta-blockers: enhanced hypotensive effect when MAOIs given with **beta-blockers**
- Bupropion: avoidance of bupropion for 2 weeks after stopping MAOIs advised by manufacturer of **bupropion**

Calcium-channel Blockers: enhanced hypotensive effect when MAOIs given with **calcium-channel blockers**

Clonidine: enhanced hypotensive effect when MAOIs given with **clonidine**

- Dapoxetine: increased risk of serotonergic effects when MAOIs given with **dapoxetine** (MAOIs should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping MAOIs)
- Diazoxide: enhanced hypotensive effect when MAOIs given with **diazoxide**
- Diuretics: enhanced hypotensive effect when MAOIs given with **diuretics**
- Dopaminergics: avoid concomitant use of non-selective MAOIs with **entacapone**; risk of hypertensive crisis when MAOIs given with **levodopa**, avoid levodopa for at least 2 weeks after stopping MAOIs; risk of hypertensive crisis when MAOIs given with **rasagiline**, avoid MAOIs for at least 2 weeks after stopping rasagiline; enhanced hypotensive effect when MAOIs given with **selegiline**—manufacturer of selegiline advises avoid concomitant use; avoid concomitant use of MAOIs with **tolcapone**
- Doxapram: MAOIs enhance effects of **doxapram**
- Histamine: avoidance of MAOIs advised by manufacturer of **histamine**
- 5HT₁-receptor Agonists: risk of CNS toxicity when MAOIs given with **rizatriptan** or **sumatriptan** (avoid rizatriptan or sumatriptan for 2 weeks after MAOIs); risk of CNS toxicity when MAOIs given with **zolmitriptan** (reduce dose of zolmitriptan)
- Methylidopa: avoidance of MAOIs advised by manufacturer of **methylidopa**
- Moxonidine: enhanced hypotensive effect when MAOIs given with **moxonidine**
- Muscle Relaxants: phenelzine enhances effects of **suxamethonium**
- Nicorandil: enhanced hypotensive effect when MAOIs given with **nicorandil**
- Nitrates: enhanced hypotensive effect when MAOIs given with **nitrates**

MAOIs (continued)

- Pholcodine: avoidance of pholcodine for 2 weeks after stopping MAOIs advised by manufacturer of **pholcodine**
- Sympathomimetics: risk of hypertensive crisis when MAOIs given with **adrenaline (epinephrine)**, **dobutamine**, **dopamine**, **methoxamine**, **noradrenaline (norepinephrine)** or **xylometazoline**; risk of hypertensive crisis when MAOIs given with **dexamfetamine**, **ephedrine**, **isometheptene**, **lisdexamfetamine**, **metaraminol**, **methylphenidate**, **phenylephrine** or **pseudoephedrine**, avoid dexamfetamine, ephedrine, isometheptene, lisdexamfetamine, metaraminol, methylphenidate, phenylephrine or pseudoephedrine for at least 2 weeks after stopping MAOIs; risk of hypertensive crisis when MAOIs given with **oxymetazoline**, some manufacturers advise avoid oxymetazoline for at least 2 weeks after stopping MAOIs
 - Tetrabenazine: risk of CNS toxicity when MAOIs given with **tetrabenazine** (avoid tetrabenazine for 2 weeks after MAOIs)
- Vasodilator Antihypertensives: enhanced hypotensive effect when MAOIs given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

MAOIs, reversible see Moclobemide**Maraviroc**

- Antibacterials: plasma concentration of maraviroc possibly increased by **clarithromycin** and **telithromycin** (consider reducing dose of maraviroc); plasma concentration of maraviroc reduced by **rifampicin**—consider increasing dose of maraviroc
- Antidepressants: plasma concentration of maraviroc possibly reduced by **St John's wort**—avoid concomitant use
- Antivirals: plasma concentration of maraviroc increased by **atazanavir**, **boceprevir**, **darunavir**, **indinavir**, **lopinavir**, **sacquinavir** and **telaprevir** (consider reducing dose of maraviroc); plasma concentration of maraviroc possibly reduced by **efavirenz**—consider increasing dose of maraviroc; plasma concentration of maraviroc possibly reduced by **etravirine**; maraviroc reduces plasma concentration of **fosamprenavir**—avoid concomitant use; plasma concentration of maraviroc increased by **ritonavir**
- Cobicistat: plasma concentration of maraviroc possibly increased by **cobicistat** (reduce dose of maraviroc)
- Orlistat: absorption of maraviroc possibly reduced by **orlistat**

Mebendazole

Ulcer-healing Drugs: metabolism of mebendazole possibly inhibited by **cimetidine** (increased plasma concentration)

Medroxyprogesterone see Progestogens**Mefenamic Acid** see NSAIDs**Mefloquine**

- Anti-arrhythmics: increased risk of ventricular arrhythmias when mefloquine given with **amiodarone**—avoid concomitant use
- Antibacterials: increased risk of ventricular arrhythmias when mefloquine given with **moxifloxacin**—avoid concomitant use; plasma concentration of mefloquine reduced by **rifampicin**—avoid concomitant use
- Antidepressants: avoidance of antimalarials advised by manufacturer of **citalopram** and **escitalopram** (risk of ventricular arrhythmias)
- Antiepileptics: mefloquine antagonises anticonvulsant effect of **antiepileptics**
- Antimalarials: avoidance of antimalarials advised by manufacturer of **artemether with lumefantrine**; increased risk of convulsions when mefloquine given with **chloroquine** and **hydroxychloroquine**; increased risk of convulsions when mefloquine

Mefloquine**Antimalarials (continued)**

- given with **quinine** (but should not prevent the use of **intravenous quinine** in severe cases)
- Antipsychotics: possible increased risk of ventricular arrhythmias when mefloquine given with **haloperidol**—avoid concomitant use; avoidance of mefloquine advised by manufacturer of **amisulpride**; increased risk of ventricular arrhythmias when mefloquine given with **pimozide**—avoid concomitant use
- Antivirals: mefloquine possibly reduces plasma concentration of **ritonavir**
- Atomoxetine: increased risk of ventricular arrhythmias when mefloquine given with **atomoxetine**
- Beta-blockers: increased risk of bradycardia when mefloquine given with **beta-blockers**
- Calcium-channel Blockers: possible increased risk of bradycardia when mefloquine given with **calcium-channel blockers**
- Cardiac Glycosides: possible increased risk of bradycardia when mefloquine given with **digoxin**
- Cytotoxics: possible increased risk of bradycardia when mefloquine given with **crizotinib**
- Histamine: avoidance of antimalarials advised by manufacturer of **histamine**
- Ivabradine: increased risk of ventricular arrhythmias when mefloquine given with **ivabradine**
- Vaccines: antimalarials inactivate **oral typhoid vaccine**—see p. 626

Megestrol see Progestogens**Melatonin** see Anxiolytics and Hypnotics**Meloxicam** see NSAIDs**Melphalan**

- Antibacterials: increased risk of melphalan toxicity when given with **nalidixic acid**
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Cardiac Glycosides: melphalan possibly reduces absorption of **digoxin tablets**
- Ciclosporin: increased risk of nephrotoxicity when melphalan given with **ciclosporin**

Memantine

- Anaesthetics, General: increased risk of CNS toxicity when memantine given with **ketamine** (manufacturer of memantine advises avoid concomitant use)
- Analgesics: increased risk of CNS toxicity when memantine given with **dextromethorphan** (manufacturer of memantine advises avoid concomitant use)
- Anticoagulants: memantine possibly enhances anticoagulant effect of **warfarin**
- Antimuscarinics: memantine possibly enhances effects of **antimuscarinics**
- Antipsychotics: memantine possibly reduces effects of **antipsychotics**
- Dopaminergics: memantine possibly enhances effects of **dopaminergics** and **selegiline**; increased risk of CNS toxicity when memantine given with **amantadine** (manufacturer of memantine advises avoid concomitant use)

Muscle Relaxants: memantine possibly modifies effects of **baclofen** and **dantrolene**

Mepacrine

Antimalarials: mepacrine increases plasma concentration of **primaquine** (increased risk of toxicity)

Meprobamate see Anxiolytics and Hypnotics**Meptazinol** see Opioid Analgesics**Mercaptopurine**

- Allopurinol: enhanced effects and increased toxicity of mercaptopurine when given with **allopurinol** (reduce dose of mercaptopurine to one quarter of usual dose)
- Aminosaliclates: possible increased risk of leucopenia when mercaptopurine given with **aminosalicylates**

Mercaptopurine (*continued*)

- Antibacterials: increased risk of haematological toxicity when mercaptopurine given with **sulfamethoxazole** (as co-trimoxazole); increased risk of haematological toxicity when mercaptopurine given with **trimethoprim** (also with co-trimoxazole)
- Anticoagulants: mercaptopurine possibly reduces anticoagulant effect of **coumarins**
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Dairy Products: plasma concentration of mercaptopurine possibly reduced by **dairy products**—manufacturer of mercaptopurine advises give at least 1 hour before or 2 hours after dairy products
- Febuxostat: avoidance of mercaptopurine advised by manufacturer of **febuxostat**

Meropenem

- Antiepileptics: carbapenems reduce plasma concentration of **valproate**—avoid concomitant use
- Probenecid: excretion of meropenem reduced by **probenecid**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Mesalazine *see* Aminosalicylates**Mestranol** *see* Oestrogens**Metaraminol** *see* Sympathomimetics**Metformin** *see* Antidiabetics**Methadone** *see* Opioid Analgesics**Methenamine**

- Antacids: avoid concomitant use of methenamine with **antacids**
- Antibacterials: increased risk of crystalluria when methenamine given with **sulfonamides**
- Diuretics: effects of methenamine antagonised by **acetazolamide**
- Potassium Salts: avoid concomitant use of methenamine with **potassium citrate**
- Sodium Citrate: avoid concomitant use of methenamine with **sodium citrate**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Methocarbamol *see* Muscle Relaxants**Methotrexate**

- Anaesthetics, General: antifolate effect of methotrexate increased by **nitrous oxide**—avoid concomitant use
- Analgesics: excretion of methotrexate probably reduced by **NSAIDs** (increased risk of toxicity); excretion of methotrexate reduced by **aspirin**, **diclofenac**, **ibuprofen**, **indometacin**, **ketoprofen**, **mefenamic acid**, **meloxicam** and **naproxen** (increased risk of toxicity)
- Antibacterials: absorption of methotrexate possibly reduced by **neomycin**; excretion of methotrexate possibly reduced by **ciprofloxacin** (increased risk of toxicity); increased risk of haematological toxicity when methotrexate given with **sulfamethoxazole** (as co-trimoxazole); increased risk of methotrexate toxicity when given with **doxycycline**, **sulfonamides** or **tetracycline**; excretion of methotrexate reduced by **penicillins** (increased risk of toxicity); increased risk of haematological toxicity when methotrexate given with **trimethoprim** (also with co-trimoxazole)
- Antiepileptics: antifolate effect of methotrexate increased by **phenytoin**
- Antimalarials: antifolate effect of methotrexate increased by **pyrimethamine**
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Cardiac Glycosides: methotrexate possibly reduces absorption of **digoxin tablets**
- Ciclosporin: risk of toxicity when methotrexate given with **ciclosporin**
- Methotrexate** (*continued*)
- Corticosteroids: possible increased risk of hepatotoxicity when **high-dose** methotrexate given with **dexamethasone**
- Cytotoxics: increased pulmonary toxicity when methotrexate given with **cisplatin**
- Diuretics: excretion of methotrexate increased by alkaline urine due to **acetazolamide**
- Leflunomide: risk of toxicity when methotrexate given with **leflunomide**
- Probenecid: excretion of methotrexate reduced by **probenecid** (increased risk of toxicity)
- Retinoids: plasma concentration of methotrexate increased by **acitretin** (also increased risk of hepatotoxicity)—avoid concomitant use
- Theophylline: methotrexate possibly increases plasma concentration of **theophylline**
- Ulcer-healing Drugs: excretion of methotrexate possibly reduced by **proton pump inhibitors** (increased risk of toxicity)
- Methoxamine** *see* Sympathomimetics
- Methyldopa**
- ACE Inhibitors: enhanced hypotensive effect when methyldopa given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when methyldopa given with **adrenergic neurone blockers**
- Alcohol: enhanced hypotensive effect when methyldopa given with **alcohol**
- Aldesleukin: enhanced hypotensive effect when methyldopa given with **aldesleukin**
- Alpha-blockers: enhanced hypotensive effect when methyldopa given with **alpha-blockers**
- Anaesthetics, General: enhanced hypotensive effect when methyldopa given with **general anaesthetics**
- Analgesics: hypotensive effect of methyldopa antagonised by **NSAIDs**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when methyldopa given with **angiotensin-II receptor antagonists**
- Antidepressants: manufacturer of methyldopa advises avoid concomitant use with **MAOIs**
- Antipsychotics: enhanced hypotensive effect when methyldopa given with **antipsychotics** (also increased risk of extrapyramidal effects)
- Anxiolytics and Hypnotics: enhanced hypotensive effect when methyldopa given with **anxiolytics and hypnotics**
- Beta-blockers: enhanced hypotensive effect when methyldopa given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with **calcium-channel blockers**
- Clonidine: enhanced hypotensive effect when methyldopa given with **clonidine**
- Corticosteroids: hypotensive effect of methyldopa antagonised by **corticosteroids**
- Diazoxide: enhanced hypotensive effect when methyldopa given with **diazoxide**
- Diuretics: enhanced hypotensive effect when methyldopa given with **diuretics**
- Dopaminergics: methyldopa antagonises antiparkinsonian effect of **dopaminergics**; increased risk of extrapyramidal side-effects when methyldopa given with **amantadine**; effects of methyldopa possibly enhanced by **entacapone**; enhanced hypotensive effect when methyldopa given with **levodopa**
- Iron: hypotensive effect of methyldopa antagonised by **oral iron**
- Lithium: neurotoxicity may occur when methyldopa given with **lithium** without increased plasma concentration of lithium
- Moxisylyte: enhanced hypotensive effect when methyldopa given with **moxisylyte**
- Moxonidine: enhanced hypotensive effect when methyldopa given with **moxonidine**

Methyldopa (*continued*)

Muscle Relaxants: enhanced hypotensive effect when methyldopa given with **baclofen** or **tizanidine**

Nitrates: enhanced hypotensive effect when methyldopa given with **nitrates**

Oestrogens: hypotensive effect of methyldopa antagonised by **oestrogens**

Prostaglandins: enhanced hypotensive effect when methyldopa given with **alprostadil**

- Sympathomimetics, Beta₂: acute hypotension reported when methyldopa given with *infusion of* **salbutamol**

Vasodilator Antihypertensives: enhanced hypotensive effect when methyldopa given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Methylphenidate *see* Sympathomimetics

Methylprednisolone *see* Corticosteroids

Methylthioninium

- Antidepressants: risk of CNS toxicity when methylthioninium given with **SSRI-related antidepressants**, **SSRIs** and **clomipramine**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration); possible risk of CNS toxicity when methylthioninium given with **mirtazapine**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)
- Anxiolytics and Hypnotics: possible risk of CNS toxicity when methylthioninium given with **buspirone**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)
- Bupropion: possible risk of CNS toxicity when methylthioninium given with **bupropion**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

Metoclopramide

Alcohol: metoclopramide possibly increases absorption of **alcohol**

Anaesthetics, General: metoclopramide enhances effects of **thiopental**

Analgesics: metoclopramide increases rate of absorption of **aspirin** (enhanced effect); effects of metoclopramide on gastro-intestinal activity antagonised by **opioid analgesics**; metoclopramide increases rate of absorption of **paracetamol**

Antidepressants: CNS toxicity reported when metoclopramide given with **SSRIs**

Antimuscarinics: effects of metoclopramide on gastro-intestinal activity antagonised by **antimuscarinics**

Antipsychotics: increased risk of extrapyramidal side-effects when metoclopramide given with **antipsychotics**

Atovaquone: metoclopramide reduces plasma concentration of **atovaquone**—avoid concomitant use

- Ciclosporin: metoclopramide increases plasma concentration of **ciclosporin**

Dopaminergics: metoclopramide antagonises hypoprolactinaemic effects of **bromocriptine** and **cabergoline**; metoclopramide antagonises antiparkinsonian effect of **pergolide**; avoidance of metoclopramide advised by manufacturer of **ropinirole** and **rotigotine** (antagonism of effect)

Muscle Relaxants: metoclopramide enhances effects of **suxamethonium**

Tetrabenazine: increased risk of extrapyramidal side-effects when metoclopramide given with **tetrabenazine**

Metolazone *see* Diuretics

Metoprolol *see* Beta-blockers

Metronidazole

Note Interactions do not apply to topical metronidazole preparations

Alcohol: disulfiram-like reaction when metronidazole given with **alcohol**

- Anticoagulants: metronidazole enhances anticoagulant effect of **coumarins**

Antiepileptics: metabolism of metronidazole accelerated by **phenobarbital** (reduced effect); metronidazole possibly inhibits metabolism of **phenytoin** (increased plasma concentration)

- Cytotoxics: metronidazole increases plasma concentration of **busulfan** (increased risk of toxicity); metronidazole inhibits metabolism of **fluorouracil** (increased toxicity)

Disulfiram: psychotic reaction reported when metronidazole given with **disulfiram**

Lithium: metronidazole increases risk of **lithium** toxicity

Mycophenolate: metronidazole possibly reduces bioavailability of **mycophenolate**

Ulcer-healing Drugs: metabolism of metronidazole inhibited by **cimetidine** (increased plasma concentration)

Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Mianserin *see* Antidepressants, Tricyclic (related)

Micafungin

Antifungals: micafungin possibly increases plasma concentration of **amphotericin**; micafungin increases plasma concentration of **itraconazole** (consider reducing dose of itraconazole)

Calcium-channel Blockers: micafungin increases plasma concentration of **nifedipine**

Ciclosporin: micafungin possibly increases plasma concentration of **ciclosporin**

Sirolimus: micafungin increases plasma concentration of **sirolimus**

Miconazole *see* Antifungals, Imidazole

Midazolam *see* Anxiolytics and Hypnotics

Mifamurtide

Analgesics: manufacturer of mifamurtide advises avoid concomitant use with high doses of **NSAIDs**

Ciclosporin: manufacturer of mifamurtide advises avoid concomitant use with **ciclosporin**

Corticosteroids: manufacturer of mifamurtide advises avoid concomitant use with **corticosteroids**

Tacrolimus: manufacturer of mifamurtide advises avoid concomitant use with **tacrolimus**

Mifepristone

Corticosteroids: mifepristone may reduce effect of **corticosteroids** (including *inhaled* corticosteroids) for 3–4 days

Milrinone *see* Phosphodiesterase Inhibitors

Minocycline *see* Tetracyclines

Minoxidil *see* Vasodilator Antihypertensives

Mirabegron

Antibacterials: avoid or reduce dose of mirabegron in hepatic or renal impairment when given with **clarithromycin**—*see* Mirabegron, BNF section 7.4.2

Antifungals: avoid or reduce dose of mirabegron in hepatic or renal impairment when given with **itraconazole**—*see* Mirabegron, BNF section 7.4.2

Antivirals: avoid or reduce dose of mirabegron in hepatic or renal impairment when given with **ritonavir**—*see* Mirabegron, BNF section 7.4.2

Beta-blockers: mirabegron increases plasma concentration of **metoprolol**

Cardiac Glycosides: mirabegron increases plasma concentration of **digoxin**—reduce initial dose of digoxin

Mirtazapine

- Alcohol: increased sedative effect when mirtazapine given with **alcohol**

Analgesics: possible increased serotonergic effects when mirtazapine given with **tramadol**

Mirtazapine (continued)

- Anticoagulants: mirtazapine enhances anticoagulant effect of **warfarin**
- Antidepressants: possible increased serotonergic effects when mirtazapine given with **fluoxetine**, **fluvoxamine** or **venlafaxine**; mirtazapine should not be started until 2 weeks after stopping **MAOIs**, also MAOIs should not be started until at least 2 weeks after stopping mirtazapine; after stopping mirtazapine do not start **moclobemide** for at least 1 week
 - Antiepileptics: plasma concentration of mirtazapine reduced by **carbamazepine** and **phenytoin**
 - Antimalarials: avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperazine with arteminol**
 - Anxiolytics and Hypnotics: increased sedative effect when mirtazapine given with **anxiolytics** and **hypnotics**
 - Atomoxetine: possible increased risk of convulsions when antidepressants given with **atomoxetine**
 - Clonidine: mirtazapine possibly antagonises hypotensive effect of **clonidine**
 - Methylthioninium: possible risk of CNS toxicity when mirtazapine given with **methylthioninium**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)
 - Ulcer-healing Drugs: plasma concentration of mirtazapine increased by **cimetidine**

Mitomycin

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Mitotane

- Anticoagulants: mitotane possibly reduces anticoagulant effect of **coumarins**
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Diuretics: manufacturer of mitotane advises avoid concomitant use of **spironolactone** (antagonism of effect)

Mitoxantrone

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Cyclosporin: excretion of mitoxantrone reduced by **cyclosporin** (increased plasma concentration)

Mivacurium see Muscle Relaxants**Mizolastine** see Antihistamines**Moclobemide**

- Analgesics: possible CNS excitation or depression (hypertension or hypotension) when moclobemide given with **dextromethorphan** or **pethidine**—avoid concomitant use; possible CNS excitation or depression (hypertension or hypotension) when moclobemide given with **opioid analgesics**—manufacturer of moclobemide advises consider reducing dose of opioid analgesics
- Antidepressants: moclobemide should not be started for at least 1 week after stopping **MAOIs**, **SSRI-related antidepressants**, **escitalopram**, **fluvoxamine**, **mirtazapine**, **paroxetine**, **sertraline**, **tricyclic-related antidepressants** or **tricyclics**; increased risk of CNS toxicity when moclobemide given with **escitalopram**, preferably avoid concomitant use; moclobemide should not be started until 5 weeks after stopping **fluoxetine**; possible increased serotonergic effects when moclobemide given with **duloxetine**
- Antimalarials: avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperazine with arteminol**
- Atomoxetine: possible increased risk of convulsions when antidepressants given with **atomoxetine**
- Bupropion: avoidance of moclobemide advised by manufacturer of **bupropion**
- Clopidogrel: moclobemide possibly reduces antiplatelet effect of **clopidogrel**

Moclobemide (continued)

- Dopaminergics: caution with moclobemide advised by manufacturer of **entacapone**; increased risk of side-effects when moclobemide given with **levodopa**; avoid concomitant use of moclobemide with **selegiline**
- 5HT₁-receptor Agonists: risk of CNS toxicity when moclobemide given with **rizatriptan** or **sumatriptan** (avoid rizatriptan or sumatriptan for 2 weeks after moclobemide); risk of CNS toxicity when moclobemide given with **zolmitriptan** (reduce dose of zolmitriptan)
- Sympathomimetics: risk of hypertensive crisis when moclobemide given with **sympathomimetics**
- Ulcer-healing Drugs: plasma concentration of moclobemide increased by **cimetidine** (halve dose of moclobemide)

Modafinil

- Antiepileptics: modafinil possibly increases plasma concentration of **phenytoin**
- Cyclosporin: modafinil reduces plasma concentration of **cyclosporin**
- Cytotoxics: modafinil possibly reduces plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid concomitant use
- Oestrogens: modafinil accelerates metabolism of **oestrogens** (reduced contraceptive effect—see p. 402)

Moexipril see ACE Inhibitors**Mometasone** see Corticosteroids**Monobactams** see Aztreonam**Montelukast** see Leukotriene Receptor Antagonists**Morphine** see Opioid Analgesics**Moxifloxacin** see Quinolones**Moxisylyte**

- ACE Inhibitors: enhanced hypotensive effect when moxisylyte given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when moxisylyte given with **adrenergic neurone blockers**
- Alpha-blockers: possible severe postural hypotension when moxisylyte given with **alpha-blockers**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when moxisylyte given with **angiotensin-II receptor antagonists**
- Beta-blockers: possible severe postural hypotension when moxisylyte given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when moxisylyte given with **calcium-channel blockers**
- Clonidine: enhanced hypotensive effect when moxisylyte given with **clonidine**
- Diazoxide: enhanced hypotensive effect when moxisylyte given with **diazoxide**
- Diuretics: enhanced hypotensive effect when moxisylyte given with **diuretics**
- Methyldopa: enhanced hypotensive effect when moxisylyte given with **methyldopa**
- Moxonidine: enhanced hypotensive effect when moxisylyte given with **moxonidine**
- Nitrates: enhanced hypotensive effect when moxisylyte given with **nitrates**
- Vasodilator Antihypertensives: enhanced hypotensive effect when moxisylyte given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Moxonidine

- ACE Inhibitors: enhanced hypotensive effect when moxonidine given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when moxonidine given with **adrenergic neurone blockers**
- Alcohol: enhanced hypotensive effect when moxonidine given with **alcohol**
- Aldesleukin: enhanced hypotensive effect when moxonidine given with **aldesleukin**

Moxonidine (*continued*)

Alpha-blockers: enhanced hypotensive effect when moxonidine given with **alpha-blockers**

Anaesthetics, General: enhanced hypotensive effect when moxonidine given with **general anaesthetics**
Analgesics: hypotensive effect of moxonidine antagonised by **NSAIDs**

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when moxonidine given with **angiotensin-II receptor antagonists**

Antidepressants: enhanced hypotensive effect when moxonidine given with **MAOIs**; hypotensive effect of moxonidine possibly antagonised by **tricyclics** (manufacturer of moxonidine advises avoid concomitant use)

Antipsychotics: enhanced hypotensive effect when moxonidine given with **phenothiazines**

Anxiolytics and Hypnotics: enhanced hypotensive effect when moxonidine given with **anxiolytics and hypnotics**; sedative effects possibly increased when moxonidine given with **benzodiazepines**

Beta-blockers: enhanced hypotensive effect when moxonidine given with **beta-blockers**

Calcium-channel Blockers: enhanced hypotensive effect when moxonidine given with **calcium-channel blockers**

Clonidine: enhanced hypotensive effect when moxonidine given with **clonidine**

Corticosteroids: hypotensive effect of moxonidine antagonised by **corticosteroids**

Diazoxide: enhanced hypotensive effect when moxonidine given with **diazoxide**

Diuretics: enhanced hypotensive effect when moxonidine given with **diuretics**

Dopaminergics: enhanced hypotensive effect when moxonidine given with **levodopa**

Methyldopa: enhanced hypotensive effect when moxonidine given with **methyldopa**

Moxisylyte: enhanced hypotensive effect when moxonidine given with **moxisylyte**

Muscle Relaxants: enhanced hypotensive effect when moxonidine given with **baclofen** or **tizanidine**

Nitrates: enhanced hypotensive effect when moxonidine given with **nitrates**

Oestrogens: hypotensive effect of moxonidine antagonised by **oestrogens**

Prostaglandins: enhanced hypotensive effect when moxonidine given with **alprostadil**

Vasodilator Antihypertensives: enhanced hypotensive effect when moxonidine given with **hydralazine**, **minoxidil** or **sodium nitropruside**

Muscle Relaxants

ACE Inhibitors: enhanced hypotensive effect when baclofen or tizanidine given with **ACE inhibitors**

Adrenergic Neurone Blockers: enhanced hypotensive effect when baclofen or tizanidine given with **adrenergic neurone blockers**

Alcohol: increased sedative effect when baclofen, methocarbamol or tizanidine given with **alcohol**

Alpha-blockers: enhanced hypotensive effect when baclofen or tizanidine given with **alpha-blockers**

- Anaesthetics, General: effects of atracurium enhanced by **ketamine**; increased risk of myocardial depression and bradycardia when suxamethonium given with **propofol**; effects of non-depolarising muscle relaxants and suxamethonium enhanced by **volatile liquid general anaesthetics**

Analgesics: excretion of baclofen possibly reduced by **NSAIDs** (increased risk of toxicity); excretion of baclofen reduced by **ibuprofen** (increased risk of toxicity); increased sedative effect when baclofen given with **fentanyl** or **morphine**

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when baclofen or tizanidine given with **angiotensin-II receptor antagonists**

Muscle Relaxants (*continued*)

Anti-arrhythmics: neuromuscular blockade enhanced and prolonged when suxamethonium given with **lidocaine**

- Antibacterials: effects of non-depolarising muscle relaxants and suxamethonium enhanced by **pipera-cillin**; plasma concentration of tizanidine increased by **ciprofloxacin** (increased risk of toxicity)—avoid concomitant use; plasma concentration of tizanidine possibly increased by **norfloxacin** (increased risk of toxicity); plasma concentration of tizanidine possibly reduced by **rifampicin**; effects of non-depolarising muscle relaxants and suxamethonium enhanced by **aminoglycosides**; effects of non-depolarising muscle relaxants and suxamethonium enhanced by **clindamycin**; effects of non-depolarising muscle relaxants and suxamethonium enhanced by **polymyxins**; effects of suxamethonium enhanced by **vancomycin**
 - Antidepressants: plasma concentration of tizanidine increased by **fluvoxamine** (increased risk of toxicity)—avoid concomitant use; effects of suxamethonium enhanced by **phenelzine**; muscle relaxant effect of baclofen enhanced by **tricyclics**
 - Antiepileptics: muscle relaxant effect of non-depolarising muscle relaxants antagonised by **carbamazepine** (accelerated recovery from neuromuscular blockade); effects of non-depolarising muscle relaxants reduced by **long-term use** of **phenytoin** (but effects of non-depolarising muscle relaxants might be increased by **acute use** of phenytoin)
- Antimalarials: effects of suxamethonium possibly enhanced by **quinine**
- Antipsychotics: effects of suxamethonium possibly enhanced by **promazine**
- Anxiolytics and Hypnotics: increased sedative effect when baclofen or tizanidine given with **anxiolytics and hypnotics**
- Beta-blockers: enhanced hypotensive effect when baclofen given with **beta-blockers**; possible enhanced hypotensive effect and bradycardia when tizanidine given with **beta-blockers**; effects of muscle relaxants enhanced by **propranolol**
- Calcium-channel Blockers: enhanced hypotensive effect when baclofen or tizanidine given with **calcium-channel blockers**; effects of non-depolarising muscle relaxants possibly enhanced by **calcium-channel blockers**; possible increased risk of ventricular arrhythmias when **intravenous** dantrolene given with **diltiazem**—manufacturer of diltiazem advises avoid concomitant use; effects of non-depolarising muscle relaxants and suxamethonium enhanced by **verapamil**; avoidance of **intravenous** dantrolene advised by manufacturer of **verapamil**
- Cardiac Glycosides: possible increased risk of bradycardia when tizanidine given with **cardiac glycosides**; risk of ventricular arrhythmias when suxamethonium given with **cardiac glycosides**
- Clonidine: enhanced hypotensive effect when baclofen or tizanidine given with **clonidine**
- Corticosteroids: effects of pancuronium and vecuronium possibly antagonised by **corticosteroids**
- Cytotoxics: effects of suxamethonium enhanced by **cyclophosphamide** and **thiotepa**
- Deferasirox: avoidance of tizanidine advised by manufacturer of **deferasirox**
- Diazoxide: enhanced hypotensive effect when baclofen or tizanidine given with **diazoxide**
- Diuretics: enhanced hypotensive effect when baclofen or tizanidine given with **diuretics**
- Dopaminergics: possible agitation, confusion and hallucinations when baclofen given with **levodopa**
- Lithium: effects of muscle relaxants enhanced by **lithium**; baclofen possibly aggravates hyperkinesia caused by **lithium**

Muscle Relaxants (*continued*)

- Magnesium (parenteral): effects of non-depolarising muscle relaxants and suxamethonium enhanced by **parenteral magnesium**
- Memantine: effects of baclofen and dantrolene possibly modified by **memantine**
- Methyldopa: enhanced hypotensive effect when baclofen or tizanidine given with **methyldopa**
- Metoclopramide: effects of suxamethonium enhanced by **metoclopramide**
- Moxonidine: enhanced hypotensive effect when baclofen or tizanidine given with **moxonidine**
- Nitrates: enhanced hypotensive effect when baclofen or tizanidine given with **nitrates**
- Oestrogens: plasma concentration of tizanidine possibly increased by **oestrogens** (increased risk of toxicity)
- Parasympathomimetics: effects of non-depolarising muscle relaxants possibly antagonised by **donepezil**; effects of suxamethonium possibly enhanced by **donepezil**; effects of non-depolarising muscle relaxants antagonised by **edrophonium**, **neostigmine**, **pyridostigmine** and **rivastigmine**; effects of suxamethonium enhanced by **edrophonium**, **galantamine**, **neostigmine**, **pyridostigmine** and **rivastigmine**
- Progestogens: plasma concentration of tizanidine possibly increased by **progestogens** (increased risk of toxicity)
- Sympathomimetics, Beta₂: effects of suxamethonium enhanced by **bambuterol**
- Vasodilator Antihypertensives: enhanced hypotensive effect when baclofen or tizanidine given with **hydralazine**; enhanced hypotensive effect when baclofen or tizanidine given with **minoxidil**; enhanced hypotensive effect when baclofen or tizanidine given with **sodium nitroprusside**

Muscle Relaxants, depolarising *see* Muscle Relaxants**Muscle Relaxants, non-depolarising** *see* Muscle Relaxants**Mycophenolate**

- Antacids: absorption of mycophenolate reduced by **antacids**
- Antibacterials: plasma concentration of mycophenolate possibly reduced by **co-amoxiclav**; bioavailability of mycophenolate possibly reduced by **metronidazole** and **norfloxacin**; plasma concentration of active metabolite of mycophenolate reduced by **rifampicin**
 - Antivirals: mycophenolate increases plasma concentration of **aciclovir**, also plasma concentration of inactive metabolite of mycophenolate increased; mycophenolate possibly increases plasma concentration of **ganciclovir**, also plasma concentration of inactive metabolite of mycophenolate possibly increased
 - Colestilan: manufacturer of colestilan advises give mycophenolate at least 1 hour before or 3 hours after **colestilan**
 - Iron: absorption of mycophenolate reduced by **oral iron**
 - Lipid-regulating Drugs: absorption of mycophenolate reduced by **colestyramine**
 - Sevelamer: plasma concentration of mycophenolate possibly reduced by **sevelamer**
- Mycophenolate Mofetil** *see* Mycophenolate
- Mycophenolate Sodium** *see* Mycophenolate
- Mycophenolic Acid** *see* Mycophenolate
- Nabumetone** *see* NSAIDs
- Nadolol** *see* Beta-blockers
- Nalidixic Acid** *see* Quinolones
- Nalmefene**
- Analgesics: manufacturer of nalmefene advises avoid concomitant use with **opioid analgesics**
- Nandrolone** *see* Anabolic Steroids

Naproxen *see* NSAIDs**Naratriptan** *see* 5HT₁-receptor Agonists (under HT)**Nateglinide** *see* Antidiabetics**Nebivolol** *see* Beta-blockers**Nefopam**

- Antidepressants: manufacturer of nefopam advises avoid concomitant use with **MAOIs**; side-effects possibly increased when nefopam given with **tricyclics**
- Antimuscarinics: increased risk of antimuscarinic side-effects when nefopam given with **antimuscarinics**

Neomycin *see* Aminoglycosides**Neostigmine** *see* Parasympathomimetics**Nevirapine**

- Analgesics: nevirapine possibly reduces plasma concentration of **methadone**
- Antibacterials: nevirapine reduces plasma concentration of **clarithromycin** (but concentration of an active metabolite increased), also plasma concentration of nevirapine increased; nevirapine possibly increases plasma concentration of **rifabutin**; plasma concentration of nevirapine reduced by **rifampicin**—avoid concomitant use
 - Anticoagulants: nevirapine may enhance or reduce anticoagulant effect of **warfarin**
 - Antidepressants: plasma concentration of nevirapine reduced by **St John's wort**—avoid concomitant use
 - Antiepileptics: plasma concentration of nevirapine reduced by **carbamazepine**
 - Antifungals: plasma concentration of nevirapine increased by **fluconazole**; nevirapine possibly reduces plasma concentration of **caspofungin** and **itraconazole**—consider increasing dose of caspofungin and itraconazole
 - Antipsychotics: nevirapine possibly reduces plasma concentration of **aripiprazole** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature)
 - Antivirals: nevirapine possibly reduces plasma concentration of **atazanavir** and **etravirine**—avoid concomitant use; manufacturer of nevirapine advises avoid concomitant use with **boceprevir** and **rilpivirine**; nevirapine possibly reduces the plasma concentration of **dolutegravir** (see Dose under Dolutegravir, p. 324); nevirapine reduces plasma concentration of **efavirenz**—avoid concomitant use; avoidance of nevirapine advised by manufacturer of **elvitegravir**; nevirapine possibly reduces plasma concentration of **fosamprenavir**—avoid unboosted fosamprenavir; nevirapine reduces plasma concentration of **indinavir**; nevirapine possibly reduces plasma concentration of **lopinavir** and **telaprevir**—consider increasing dose of lopinavir and telaprevir; increased risk of granulocytopenia when nevirapine given with **zidovudine**
 - Cobicistat: manufacturer of cobicistat advises avoid concomitant use with **cobicistat**
 - Oestrogens: nevirapine accelerates metabolism of **oestrogens** (reduced contraceptive effect—see p. 402)
 - Orlistat: absorption of nevirapine possibly reduced by **orlistat**
 - Progestogens: nevirapine accelerates metabolism of **progestogens** (reduced contraceptive effect—see p. 402)
- Nicardipine** *see* Calcium-channel Blockers
- Nicorandil**
- Alcohol: hypotensive effect of nicorandil possibly enhanced by **alcohol**
- Antidepressants: enhanced hypotensive effect when nicorandil given with **MAOIs**; hypotensive effect of nicorandil possibly enhanced by **tricyclics**
- Sildenafil: hypotensive effect of nicorandil significantly enhanced by **sildenafil** (avoid concomitant use)

Nicorandil (*continued*)

- Tadalafil: hypotensive effect of nicorandil significantly enhanced by **•tadalafil** (avoid concomitant use)
- Vardenafil: possible increased hypotensive effect when nicorandil given with **•vardenafil**—avoid concomitant use

Vasodilator Antihypertensives: possible enhanced hypotensive effect when nicorandil given with **hydralazine, minoxidil or sodium nitroprusside**

Nicotine

Anti-arrhythmics: nicotine possibly enhances effects of **adenosine**

Nicotinic Acid

Note Interactions apply to lipid-regulating doses of nicotinic acid

- Lipid-regulating Drugs: increased risk of myopathy when nicotinic acid given with **•statins** (applies to lipid regulating doses of nicotinic acid)

Nifedipine *see* Calcium-channel Blockers

Nilotinib

- Antibacterials: manufacturer of nilotinib advises avoid concomitant use with **•clarithromycin** and **•telithromycin**; plasma concentration of nilotinib reduced by **•rifampicin**—avoid concomitant use
- Antifungals: manufacturer of nilotinib advises avoid concomitant use with **•voriconazole**
- Antipsychotics: avoid concomitant use of cytotoxics with **•clozapine** (increased risk of agranulocytosis)
- Antivirals: avoidance of nilotinib advised by manufacturer of **•boceprevir**; plasma concentration of nilotinib possibly increased by **ritonavir**—manufacturer of nilotinib advises avoid concomitant use
- Anxiolytics and Hypnotics: nilotinib increases plasma concentration of **midazolam**
- Grapefruit Juice: manufacturer of nilotinib advises avoid concomitant use with **•grapefruit juice**

Nimodipine *see* Calcium-channel Blockers

Nitrates

- ACE Inhibitors: enhanced hypotensive effect when nitrates given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when nitrates given with **adrenergic neurone blockers**
- Alcohol: enhanced hypotensive effect when nitrates given with **alcohol**
- Aldesleukin: enhanced hypotensive effect when nitrates given with **aldesleukin**
- Alpha-blockers: enhanced hypotensive effect when nitrates given with **alpha-blockers**
- Anaesthetics, General: enhanced hypotensive effect when nitrates given with **general anaesthetics**
- Analgesics: hypotensive effect of nitrates antagonised by **NSAIDs**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when nitrates given with **angiotensin-II receptor antagonists**
- Anti-arrhythmics: effects of sublingual tablets of nitrates reduced by **disopyramide** (failure to dissolve under tongue owing to dry mouth)
- Anticoagulants: *infusion* of glyceryl trinitrate reduces anticoagulant effect of **•heparins**
- Antidepressants: enhanced hypotensive effect when nitrates given with **MAOIs**; effects of sublingual tablets of nitrates possibly reduced by **tricyclic-related antidepressants** (failure to dissolve under tongue owing to dry mouth); effects of sublingual tablets of nitrates reduced by **tricyclics** (failure to dissolve under tongue owing to dry mouth)
- Antimuscarinics: effects of sublingual tablets of nitrates possibly reduced by **antimuscarinics** (failure to dissolve under tongue owing to dry mouth)
- Antipsychotics: enhanced hypotensive effect when nitrates given with **phenothiazines**
- Anxiolytics and Hypnotics: enhanced hypotensive effect when nitrates given with **anxiolytics and hypnotics**

Nitrates (*continued*)

- Beta-blockers: enhanced hypotensive effect when nitrates given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when nitrates given with **calcium-channel blockers**
- Clonidine: enhanced hypotensive effect when nitrates given with **clonidine**
- Corticosteroids: hypotensive effect of nitrates antagonised by **corticosteroids**
- Diazoxide: enhanced hypotensive effect when nitrates given with **diazoxide**
- Diuretics: enhanced hypotensive effect when nitrates given with **diuretics**
- Dopaminergics: enhanced hypotensive effect when nitrates given with **levodopa**
- Methyldopa: enhanced hypotensive effect when nitrates given with **methyldopa**
- Moxisylyte: enhanced hypotensive effect when nitrates given with **moxisylyte**
- Moxonidine: enhanced hypotensive effect when nitrates given with **moxonidine**
- Muscle Relaxants: enhanced hypotensive effect when nitrates given with **baclofen** or **tizanidine**
- Oestrogens: hypotensive effect of nitrates antagonised by **oestrogens**
- Prostaglandins: enhanced hypotensive effect when nitrates given with **alprostadil**
- Sildenafil: hypotensive effect of nitrates significantly enhanced by **•sildenafil** (avoid concomitant use)
- Tadalafil: hypotensive effect of nitrates significantly enhanced by **•tadalafil** (avoid concomitant use)
- Vardenafil: possible increased hypotensive effect when nitrates given with **•vardenafil**—avoid concomitant use
- Vasodilator Antihypertensives: enhanced hypotensive effect when nitrates given with **hydralazine, minoxidil or sodium nitroprusside**

Nitrazepam *see* Anxiolytics and Hypnotics

Nitrofurantoin

- Antacids: absorption of nitrofurantoin reduced by **oral magnesium salts** (as magnesium trisilicate)
- Antibacterials: nitrofurantoin possibly antagonises effects of **nalidixic acid**
- Probenecid: excretion of nitrofurantoin reduced by **probenecid** (increased risk of side-effects)
- Sulfinpyrazone: excretion of nitrofurantoin reduced by **sulfinpyrazone** (increased risk of toxicity)
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Nitroimidazoles *see* Metronidazole and Tinidazole

Nitrous Oxide *see* Anaesthetics, General

Nizatidine *see* Histamine H₂-antagonists

Nomegestrol *see* Progestogens

Noradrenaline (norepinephrine) *see* Sympathomimetics

Norelgestromin *see* Progestogens

Norepinephrine (noradrenaline) *see* Sympathomimetics

Norethisterone *see* Progestogens

Norfloracin *see* Quinolones

Norgestimate *see* Progestogens

Norgestrel *see* Progestogens

Nortriptyline *see* Antidepressants, Tricyclic

NSAIDs

Note *See also* Aspirin. Interactions do not generally apply to topical NSAIDs

- ACE Inhibitors: increased risk of renal impairment when NSAIDs given with **ACE inhibitors**, also hypotensive effect antagonised

Adrenergic Neurone Blockers: NSAIDs antagonise hypotensive effect of **adrenergic neurone blockers**

Aliskiren: NSAIDs possibly antagonise hypotensive effect of **aliskiren**

NSAIDs (continued)

Alpha-blockers: NSAIDs antagonise hypotensive effect of **alpha-blockers**

- Analgesics: avoid concomitant use of NSAIDs with **NSAIDs** or **aspirin** (increased side-effects); avoid concomitant use of NSAIDs with **ketorolac** (increased side-effects and haemorrhage); ibuprofen possibly reduces antiplatelet effect of **aspirin**

Angiotensin-II Receptor Antagonists: increased risk of renal impairment when NSAIDs given with **angiotensin-II receptor antagonists**, also hypotensive effect antagonised

Antacids: absorption of acemetacin possibly reduced by **antacids**

- Antibacterials: indometacin possibly increases plasma concentration of **amikacin** and **gentamicin** in neonates; plasma concentration of celecoxib, diclofenac and etoricoxib reduced by **rifampicin**; possible increased risk of convulsions when NSAIDs given with **quinolones**

- Anticoagulants: increased risk of haemorrhage when **intravenous diclofenac** given with **anticoagulants** (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when ketorolac given with **anticoagulants** (avoid concomitant use, including low-dose heparins); NSAIDs possibly enhance anticoagulant effect of **coumarins** and **phenindione**; possible increased risk of bleeding when NSAIDs given with **dabigatran** or **heparins**

- Antidepressants: increased risk of bleeding when NSAIDs given with **SSRIs** or **venlafaxine**

- Antidiabetics: NSAIDs possibly enhance effects of **sulfonylureas**

Antiepileptics: acemetacin possibly reduces excretion of **phenytoin** (increased risk of toxicity)

Antifungals: plasma concentration of parecoxib increased by **fluconazole** (reduce dose of parecoxib); plasma concentration of celecoxib increased by **fluconazole** (halve dose of celecoxib); plasma concentration of flurbiprofen and ibuprofen increased by **fluconazole**; plasma concentration of diclofenac and ibuprofen increased by **voriconazole**

Antipsychotics: possible severe drowsiness when acemetacin or indometacin given with **haloperidol**

- Antivirals: plasma concentration of NSAIDs possibly increased by **ritonavir**; plasma concentration of piroxicam increased by **ritonavir** (risk of toxicity)—avoid concomitant use; increased risk of haematological toxicity when NSAIDs given with **zidovudine**

Beta-blockers: NSAIDs antagonise hypotensive effect of **beta-blockers**

Calcium-channel Blockers: NSAIDs antagonise hypotensive effect of **calcium-channel blockers**

Cardiac Glycosides: NSAIDs possibly increase plasma concentration of **cardiac glycosides**, also possible exacerbation of heart failure and reduction of renal function

- Ciclosporin: increased risk of nephrotoxicity when NSAIDs given with **ciclosporin**; plasma concentration of diclofenac increased by **ciclosporin** (halve dose of diclofenac)

Clonidine: NSAIDs antagonise hypotensive effect of **clonidine**

Clopidogrel: increased risk of bleeding when NSAIDs given with **clopidogrel**

Corticosteroids: increased risk of gastro-intestinal bleeding and ulceration when NSAIDs given with **corticosteroids**

- Cytotoxics: NSAIDs probably reduce excretion of **methotrexate** (increased risk of toxicity); diclofenac, ibuprofen, indometacin, ketoprofen, meloxicam and naproxen reduce excretion of **methotrexate** (increased risk of toxicity); NSAIDs possibly reduce renal excretion of **pemetrexed**—consult product literature; increased risk of bleeding when

NSAIDs

- **Cytotoxics (continued)**

NSAIDs given with **erlotinib**; avoidance of mefenamic acid advised by manufacturer of **regorafenib**
Desmopressin: indometacin enhances effects of **desmopressin**

Diazoxide: NSAIDs antagonise hypotensive effect of **diazoxide**

- Dimethyl sulfoxide: avoid concomitant use of sulindac with **dimethyl sulfoxide**

- Diuretics: risk of nephrotoxicity of NSAIDs increased by **diuretics**, also antagonism of diuretic effect; indometacin and ketorolac antagonise effects of **diuretics**; excretion of acemetacin possibly increased by **furosemide**; NSAIDs possibly antagonise diuretic effect of **potassium canrenoate**; occasional reports of reduced renal function when indometacin given with **triamterene**—avoid concomitant use; increased risk of hyperkalaemia when indometacin given with **potassium-sparing diuretics** and **aldosterone antagonists**; possible increased risk of hyperkalaemia when NSAIDs given with **potassium-sparing diuretics** and **aldosterone antagonists**

Iloprost: increased risk of bleeding when NSAIDs given with **iloprost**

Lipid-regulating Drugs: excretion of meloxicam increased by **colestyramine**

- Lithium: NSAIDs reduce excretion of **lithium** (increased risk of toxicity); ketorolac reduces excretion of **lithium** (increased risk of toxicity)—avoid concomitant use

Methyldopa: NSAIDs antagonise hypotensive effect of **methyldopa**

Mifamurtide: avoidance of high doses of NSAIDs advised by manufacturer of **mifamurtide**

Moxonidine: NSAIDs antagonise hypotensive effect of **moxonidine**

Muscle Relaxants: ibuprofen reduces excretion of **baclofen** (increased risk of toxicity); NSAIDs possibly reduce excretion of **baclofen** (increased risk of toxicity)

Nitrates: NSAIDs antagonise hypotensive effect of **nitrates**

Oestrogens: etoricoxib increases plasma concentration of **ethinylestradiol**

Penicillamine: possible increased risk of nephrotoxicity when NSAIDs given with **penicillamine**

- Pentoxifylline: possible increased risk of bleeding when NSAIDs given with **pentoxifylline**; increased risk of bleeding when ketorolac given with **pentoxifylline** (avoid concomitant use)

Prasugrel: possible increased risk of bleeding when NSAIDs given with **prasugrel**

- Probenecid: excretion of acemetacin, dextketoprofen, indometacin, ketoprofen and naproxen reduced by **probenecid** (increased plasma concentration); excretion of ketorolac reduced by **probenecid** (increased plasma concentration)—avoid concomitant use

- Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs given with **tacrolimus**; increased risk of nephrotoxicity when ibuprofen given with **tacrolimus**

Vasodilator Antihypertensives: NSAIDs antagonise hypotensive effect of **hydralazine**, **minoxidil** and **sodium nitroprusside**

Octreotide

Antidiabetics: octreotide possibly reduces requirements for **antidiabetics**

- Ciclosporin: octreotide reduces plasma concentration of **ciclosporin**

Dopaminergics: octreotide increases plasma concentration of **bromocriptine**

Ulcer-healing Drugs: octreotide possibly delays absorption of **cimetidine**

Oestrogens

Note Interactions of combined oral contraceptives may also apply to combined contraceptive patches and vaginal rings, see p. 402

ACE Inhibitors: oestrogens antagonise hypotensive effect of **ACE inhibitors**

Adrenergic Neurone Blockers: oestrogens antagonise hypotensive effect of **adrenergic neurone blockers**

Alpha-blockers: oestrogens antagonise hypotensive effect of **alpha-blockers**

Analgesics: plasma concentration of ethinylestradiol increased by **etoricoxib**

Angiotensin-II Receptor Antagonists: oestrogens antagonise hypotensive effect of **angiotensin-II receptor antagonists**

- Antibacterials: plasma concentration of estradiol increased by **erythromycin**; metabolism of oestrogens accelerated by **rifamycins** (reduced contraceptive effect—see p. 402)
- Anticoagulants: oestrogens may enhance or reduce anticoagulant effect of **coumarins**; oestrogens antagonise anticoagulant effect of **phenindione**
- Antidepressants: contraceptive effect of oestrogens reduced by **St John's wort** (avoid concomitant use); oestrogens antagonise antidepressant effect of **tricyclics** (but side-effects of tricyclics possibly increased due to increased plasma concentration)
- Antidiabetics: oestrogens antagonise hypoglycaemic effect of **antidiabetics**
- Antiepileptics: metabolism of oestrogens accelerated by **carbamazepine**, **eslicarbazepine**, **oxcarbazepine**, **phenobarbital**, **phenytoin**, **rufinamide** and **topiramate** (reduced contraceptive effect—see p. 402); oestrogens reduce plasma concentration of **lamotrigine**—consider increasing dose of lamotrigine; ethinylestradiol possibly reduces plasma concentration of **valproate**
- Antifungals: oestrogens increase plasma concentration of **voriconazole**; anecdotal reports of contraceptive failure and menstrual irregularities when oestrogens given with **griseofulvin**; anecdotal reports of contraceptive failure when oestrogens given with **imidazoles**; occasional reports of breakthrough bleeding when oestrogens (used for contraception) given with **terbinafine**
- Antivirals: plasma concentration of ethinylestradiol increased by **atazanavir**; metabolism of oestrogens accelerated by **nevirapine** and **ritonavir** (reduced contraceptive effect—see p. 402); plasma concentration of ethinylestradiol possibly reduced by **telaprevir**—manufacturer of telaprevir advises additional contraceptive precautions
- Anxiolytics and Hypnotics: oestrogens possibly increase plasma concentration of **chlordiazepoxide**, **diazepam** and **nitrazepam**; oestrogens possibly reduce plasma concentration of **lorazepam**, **oxazepam** and **temazepam**; oestrogens increase plasma concentration of **melatonin**
- Aprepitant: possible contraceptive failure of hormonal contraceptives containing oestrogens when given with **aprepitant** (alternative contraception recommended)
- Beta-blockers: oestrogens antagonise hypotensive effect of **beta-blockers**
- Bosentan: possible contraceptive failure of hormonal contraceptives containing oestrogens when given with **bosentan** (alternative contraception recommended)
- Calcium-channel Blockers: oestrogens antagonise hypotensive effect of **calcium-channel blockers**
- Ciclosporin: oestrogens possibly increase plasma concentration of **ciclosporin**
- Clonidine: oestrogens antagonise hypotensive effect of **clonidine**

Oestrogens (continued)

- Cobiciclat: metabolism of oestrogens accelerated by **cobiciclat** (reduced contraceptive effect—see p. 402)
- Corticosteroids: oral contraceptives containing oestrogens increase plasma concentration of **corticosteroids**
- Cytotoxics: possible reduction in contraceptive effect of oestrogens advised by manufacturer of **crizotinib** and **vemurafenib**; possible reduced contraceptive effect of hormonal contraceptives containing oestrogens advised by manufacturer of **dabrafenib** (alternative contraception recommended)
- Diuretics: oestrogens antagonise diuretic effect of **diuretics**
- Dopaminergics: oestrogens increase plasma concentration of **ropinirole**; oestrogens increase plasma concentration of **selegiline**—manufacturer of selegiline advises avoid concomitant use
- Lipid-regulating Drugs: absorption of ethinylestradiol reduced by **colesevelam**; plasma concentration of ethinylestradiol increased by **atorvastatin** and **rosuvastatin**
- Methylidopa: oestrogens antagonise hypotensive effect of **methylidopa**
- Modafinil: metabolism of oestrogens accelerated by **modafinil** (reduced contraceptive effect—see p. 402)
- Moxonidine: oestrogens antagonise hypotensive effect of **moxonidine**
- Muscle Relaxants: oestrogens possibly increase plasma concentration of **tizanidine** (increased risk of toxicity)
- Nitrates: oestrogens antagonise hypotensive effect of **nitrates**
- Somatropin: oestrogens (when used as oral replacement therapy) may increase dose requirements of **somatropin**
- Tacrolimus: ethinylestradiol possibly increases plasma concentration of **tacrolimus**
- Teriflunomide: plasma concentration of ethinylestradiol increased by **teriflunomide**
- Theophylline: oestrogens increase plasma concentration of **theophylline** (consider reducing dose of theophylline)
- Thyroid Hormones: oestrogens may increase requirements for **thyroid hormones** in hypothyroidism
- Vasodilator Antihypertensives: oestrogens antagonise hypotensive effect of **hydralazine**, **minoxidil** and **sodium nitroprusside**
- **Oestrogens, conjugated** *see* Oestrogens
- **Ofloxacin** *see* Quinolones
- **Olanzapine** *see* Antipsychotics
- **Olmesartan** *see* Angiotensin-II Receptor Antagonists
- **Olalazine** *see* Aminosaliclates
- **Omeprazole** *see* Proton Pump Inhibitors
- **Onandasetron** *see* 5HT₃-receptor Antagonists (under HT)
- **Opioid Analgesics**
 - Alcohol: enhanced hypotensive and sedative effects when opioid analgesics given with **alcohol**
 - Anaesthetics, General: fentanyl inhibits metabolism of **etomidate** (consider reducing dose of etomidate); opioid analgesics possibly enhance effects of **intravenous general anaesthetics** and **volatile liquid general anaesthetics**
 - Antibacterials: plasma concentration of fentanyl possibly increased by **clarithromycin**; plasma concentration of alfentanil increased by **erythromycin**; metabolism of alfentanil, codeine, fentanyl, methadone and morphine accelerated by **rifampicin** (reduced effect); metabolism of oxycodone possibly accelerated by **rifampicin**; manufacturer of pethidine advises avoid concomitant use with **isoniazid**; possible increased risk of ventricular arrhythmias when

Opioid Analgesics

- **Antibacterials** (*continued*)
methadone given with •**telithromycin**; metabolism of oxycodone inhibited by **telithromycin**
- **Anticoagulants**: tramadol enhances anticoagulant effect of •**coumarins**
- **Antidepressants**: plasma concentration of methadone possibly increased by **fluoxetine**, **fluvoxamine**, **paroxetine** and **sertraline**; possible increased serotonergic effects when pethidine or tramadol given with **duloxetine**; possible increased serotonergic effects when tramadol given with **mirtazapine** or **venlafaxine**; possible increased serotonergic effects and increased risk of convulsions when tramadol given with •**MAOIs**—some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs; CNS excitation or depression (hypertension or hypotension) when pethidine given with •**MAOIs**—avoid concomitant use and for 2 weeks after stopping MAOIs; possible increased serotonergic effects when fentanyl given with **MAOIs**, **SSRI-related antidepressants** or **SSRIs**; possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with •**MAOIs**—some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs; possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with •**moclobemide**—manufacturer of moclobemide advises consider reducing dose of opioid analgesics; possible CNS excitation or depression (hypertension or hypotension) when dextromethorphan or pethidine given with •**moclobemide**—avoid concomitant use; increased risk of CNS toxicity when tramadol given with •**SSRIs** or •**tricyclics**; plasma concentration of methadone possibly reduced by **St John's wort**; sedative effects possibly increased when opioid analgesics given with **tricyclics**
- **Antiepileptics**: metabolism of fentanyl possibly accelerated by **carbamazepine** and **phenytoin** (reduced effect); dextropropoxyphene enhances effects of •**carbamazepine**; effects of tramadol reduced by **carbamazepine**; plasma concentration of methadone reduced by **carbamazepine** and **phenobarbital**; morphine increases bioavailability of **gabapentin**; metabolism of methadone accelerated by **phenytoin** (reduced effect and risk of withdrawal effects); possible increased risk of pethidine toxicity when given with •**phenytoin**
- **Antifungals**: metabolism of alfentanil inhibited by **fluconazole** (risk of prolonged or delayed respiratory depression); plasma concentration of methadone increased by **fluconazole**; metabolism of alfentanil possibly inhibited by **itraconazole**; plasma concentration of methadone possibly increased by •**itraconazole** (increased risk of ventricular arrhythmias); plasma concentration of oxycodone increased by **itraconazole** and •**voriconazole**; plasma concentration of alfentanil and methadone increased by •**voriconazole** (consider reducing dose of alfentanil and methadone); plasma concentration of fentanyl possibly increased by •**triazoles**
- **Antihistamines**: sedative effects possibly increased when opioid analgesics given with •**sedating antihistamines**
- **Antimalarials**: avoidance of methadone advised by manufacturer of •**piperaquine** with **artemisinin** (possible risk of ventricular arrhythmias)
Antimuscarinics: possible increased risk of antimuscarinic side-effects when codeine given with **antimuscarinics**
- **Antipsychotics**: enhanced hypotensive and sedative effects when opioid analgesics given with **antipsychotics**; increased risk of ventricular arrhythmias when methadone given with •**antipsychotics** that prolong the QT interval; increased risk of con-

Opioid Analgesics

- **Antipsychotics** (*continued*)
vulsions when tramadol given with **antipsychotics**; increased risk of ventricular arrhythmias when methadone given with •**amisulpride**—avoid concomitant use
- **Antivirals**: plasma concentration of methadone possibly reduced by **abacavir**, **nevirapine** and **rilpivirine**; plasma concentration of methadone possibly affected by **boceprevir**; possible increased risk of prolonged sedation and respiratory depression when buprenorphine given with **boceprevir**; methadone possibly reduces plasma concentration of **didanosine**; plasma concentration of methadone reduced by **efavirenz**, **fosamprenavir** and **ritonavir**; plasma concentration of morphine possibly reduced by **ritonavir**; plasma concentration of alfentanil and fentanyl increased by •**ritonavir**; plasma concentration of dextropropoxyphene increased by •**ritonavir** (risk of toxicity)—avoid concomitant use; plasma concentration of buprenorphine possibly increased by **ritonavir**; plasma concentration of pethidine reduced by •**ritonavir**, but plasma concentration of toxic pethidine metabolite increased (avoid concomitant use); increased risk of ventricular arrhythmias when alfentanil, fentanyl or methadone given with •**sacquinavir**—avoid concomitant use; caution with methadone advised by manufacturer of •**telaprevir** (risk of ventricular arrhythmias); buprenorphine possibly reduces plasma concentration of **tipranavir**; methadone possibly increases plasma concentration of **zidovudine**
- **Anxiolytics and Hypnotics**: increased sedative effect when opioid analgesics given with **anxiolytics** and **hypnotics**; fentanyl possibly inhibits metabolism of **midazolam**
- **Atomoxetine**: increased risk of ventricular arrhythmias when methadone given with •**atomoxetine**; possible increased risk of convulsions when tramadol given with **atomoxetine**
- **Beta-blockers**: morphine possibly increases plasma concentration of **esmolol**
- **Calcium-channel Blockers**: metabolism of alfentanil inhibited by **diltiazem** (risk of prolonged or delayed respiratory depression)
- **Cytotoxics**: possible increased risk of ventricular arrhythmias when methadone given with •**bosutinib**; caution with alfentanil and fentanyl advised by manufacturer of •**crizotinib**; possible increased risk of ventricular arrhythmias when methadone given with •**vandetanib**—avoid concomitant use
- **Dapoxetine**: possible increased risk of serotonergic effects when tramadol given with •**dapoxetine** (manufacturer of dapoxetine advises tramadol should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tramadol)
- **Domperidone**: opioid analgesics antagonise effects of **domperidone** on gastro-intestinal activity
- **Dopaminergics**: risk of CNS toxicity when pethidine given with •**rasagiline** (avoid pethidine for 2 weeks after rasagiline); avoid concomitant use of dextromethorphan with •**rasagiline**; hyperpyrexia and CNS toxicity reported when pethidine given with •**selegiline** (avoid concomitant use); avoidance of opioid analgesics advised by manufacturer of **selegiline**
- **5HT₂-receptor Antagonists**: effects of tramadol possibly antagonised by **ondansetron**
- **Mementine**: increased risk of CNS toxicity when dextromethorphan given with •**mementine** (manufacturer of mementine advises avoid concomitant use)
- **Metoclopramide**: opioid analgesics antagonise effects of **metoclopramide** on gastro-intestinal activity

Opioid Analgesics (*continued*)

Muscle Relaxants: increased sedative effect when fentanyl or morphine given with **baclofen**

- Nalmefene: avoidance of opioid analgesics advised by manufacturer of **nalmefene**
 - Sodium Oxybate: opioid analgesics enhance effects of **sodium oxybate** (avoid concomitant use)
- Ulcer-healing Drugs: metabolism of opioid analgesics inhibited by **cimetidine** (increased plasma concentration)

Orlistat

Anti-arrhythmics: orlistat possibly reduces plasma concentration of **amiodarone**

Anticoagulants: manufacturer of orlistat recommends monitoring anticoagulant effect of **coumarins**

Antidiabetics: manufacturer of orlistat advises avoid concomitant use with **acarbose**

- Antiepileptics: possible increased risk of convulsions when orlistat given with **antiepileptics**
- Antivirals: orlistat possibly reduces absorption of
 - **abacavir**, **atazanavir**, **darunavir**, **didanosine**, **efavirenz**, **elvitegravir**, **emtricitabine**, **enfuvirtide**, **etravirine**, **fosamprenavir**, **indinavir**, **lamivudine**, **lopinavir**, **maraviroc**, **nevirapine**, **raltegravir**, **rilpivirine**, **ritonavir**, **saquinavir**, **stavudine**, **tenofovir**, **tipranavir** and **zidovudine**
- Ciclosporin: orlistat possibly reduces absorption of **ciclosporin**

Thyroid Hormones: possible increased risk of hypothyroidism when orlistat given with **levothyroxine**

Orphenadrine *see* Antimuscarinics

Oxaliplatin *see* Platinum Compounds

Oxandrolone *see* Anabolic Steroids

Oxazepam *see* Anxiolytics and Hypnotics

Oxcarbazepine

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIs** and **tricyclics** (convulsive threshold lowered)

- Antiepileptics: oxcarbazepine sometimes reduces plasma concentration of **carbamazepine** (but concentration of an active metabolite of carbamazepine may be increased), also plasma concentration of an active metabolite of oxcarbazepine often reduced; avoidance of oxcarbazepine advised by manufacturer of **eslicarbazepine**; oxcarbazepine reduces plasma concentration of **perampanel** (see Dose under Perampanel, p. 226); oxcarbazepine increases plasma concentration of **phenobarbital** and **phenytoin**, also plasma concentration of an active metabolite of oxcarbazepine reduced; plasma concentration of an active metabolite of oxcarbazepine sometimes reduced by **valproate**

- Antimalarials: anticonvulsant effect of antiepileptics antagonised by **mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **antipsychotics** (convulsive threshold lowered)
- Antivirals: avoidance of oxcarbazepine advised by manufacturer of **dolutegravir** and **sofosbuvir**; avoidance of oxcarbazepine advised by manufacturer of **rilpivirine** (plasma concentration of rilpivirine possibly reduced)

Ciclosporin: oxcarbazepine possibly reduces plasma concentration of **ciclosporin**

- Clopidogrel: oxcarbazepine possibly reduces antiplatelet effect of **clopidogrel**
- Cytotoxics: oxcarbazepine reduces plasma concentration of **imatinib**—avoid concomitant use
- Oestrogens: oxcarbazepine accelerates metabolism of **oestrogens** (reduced contraceptive effect—see p. 402)

Oxcarbazepine (*continued*)

- Orlistat: possible increased risk of convulsions when antiepileptics given with **orlistat**
- Progestogens: oxcarbazepine accelerates metabolism of **progestogens** (reduced contraceptive effect—see p. 402)

Oxprenolol *see* Beta-blockers

Oxybutynin *see* Antimuscarinics

Oxycodone *see* Opioid Analgesics

Oxymetazoline *see* Sympathomimetics

Oxytetracycline *see* Tetracyclines

Oxytocin

Anaesthetics, General: oxytocic effect possibly reduced, also enhanced hypotensive effect and risk of arrhythmias when oxytocin given with **volatile liquid general anaesthetics**

Prostaglandins: uterotonic effect of oxytocin potentiated by **prostaglandins**

Sympathomimetics: risk of hypertension when oxytocin given with vasoconstrictor **sympathomimetics** (due to enhanced vasopressor effect)

Paclitaxel

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Antivirals: plasma concentration of paclitaxel increased by **ritonavir**

- Cytotoxics: increased risk of neutropenia when paclitaxel given with **lapatinib**

Paliperidone *see* Antipsychotics

Pamidronate Disodium *see* Bisphosphonates

Pancreatin

Antidiabetics: pancreatin antagonises hypoglycaemic effect of **acarbose**

Pancuronium *see* Muscle Relaxants

Pantoprazole *see* Proton Pump Inhibitors

Papaveretum *see* Opioid Analgesics

Paracetamol

Anticoagulants: prolonged regular use of paracetamol possibly enhances anticoagulant effect of **coumarins**

Antidiabetics: absorption of paracetamol possibly reduced when given 1 to 4 hours after **lixisenatide**

Antiepileptics: metabolism of paracetamol possibly accelerated by **carbamazepine**, **phenobarbital** and **phenytoin** (also isolated reports of hepatotoxicity)

Cytotoxics: paracetamol possibly inhibits metabolism of **intravenous busulfan** (manufacturer of **intravenous busulfan** advises caution within 72 hours of paracetamol); caution with paracetamol advised by manufacturer of **imatinib**

Lipid-regulating Drugs: absorption of paracetamol reduced by **colestyramine**

Metoclopramide: rate of absorption of paracetamol increased by **metoclopramide**

Paraldehyde

- Alcohol: increased sedative effect when paraldehyde given with **alcohol**
- Disulfiram: risk of toxicity when paraldehyde given with **disulfiram**

Parasympathomimetics

Anti-arrhythmics: effects of neostigmine and pyridostigmine possibly antagonised by **propafenone**

- Antibacterials: plasma concentration of galantamine increased by **erythromycin**; effects of neostigmine and pyridostigmine antagonised by **aminoglycosides**; effects of neostigmine and pyridostigmine antagonised by **clindamycin**; effects of neostigmine and pyridostigmine antagonised by **polymyxins**

Antidepressants: plasma concentration of galantamine increased by **paroxetine**

Antimalarials: effects of neostigmine and pyridostigmine may be diminished because of potential for **chloroquine** and **hydroxychloroquine** to increase symptoms of myasthenia gravis

Antimuscarinics: effects of parasympathomimetics antagonised by **antimuscarinics**

Parasympathomimetics (continued)

Beta-blockers: increased risk of arrhythmias when pilocarpine given with **beta-blockers**; effects of neostigmine and pyridostigmine antagonised by **propranolol**

Cytotoxics: possible increased risk of bradycardia when pilocarpine given with **crizotinib**

Lithium: effects of neostigmine antagonised by **lithium**

Muscle Relaxants: donepezil possibly enhances effects of **suxamethonium**; edrophonium, galantamine, neostigmine, pyridostigmine and rivastigmine enhance effects of **suxamethonium**; edrophonium, neostigmine, pyridostigmine and rivastigmine antagonise effects of **non-depolarising muscle relaxants**; donepezil possibly antagonises effects of **non-depolarising muscle relaxants**

Paracetamol see NSAIDs**Paricalcitol** see Vitamins**Paroxetine** see Antidepressants, SSRI**Pasireotide**

Antidiabetics: pasireotide possibly reduces requirements for **antidiabetics**

Antimuscarinics: possible increased risk of bradycardia when pasireotide given with **ipratropium** or **oxybutynin**

Beta-blockers: possible increased risk of bradycardia when pasireotide given with **carteolol**, **metoprolol**, **propranolol** or **sotalol**

Calcium-channel Blockers: possible increased risk of bradycardia when pasireotide given with **diltiazem** or **verapamil**

- Ciclosporin: pasireotide possibly reduces plasma concentration of **ciclosporin**

Pazopanib

- Antibacterials: plasma concentration of pazopanib possibly increased by **clarithromycin** and **tetracycline** (reduce dose of pazopanib); plasma concentration of pazopanib possibly reduced by **rifampicin**

- Antifungals: plasma concentration of pazopanib possibly increased by **itraconazole** and **voriconazole** (reduce dose of pazopanib)

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

- Antivirals: plasma concentration of pazopanib possibly increased by **atazanavir**, **indinavir** and **ritonavir** (reduce dose of pazopanib); avoidance of pazopanib advised by manufacturer of **bocoprevir**; increased risk of ventricular arrhythmias when pazopanib given with **saquinavir**—avoid concomitant use

Cytotoxics: plasma concentration of pazopanib increased by **lapatinib**

- Grapefruit Juice: manufacturer of pazopanib advises avoid concomitant use with **grapefruit juice**

Ulcer-healing Drugs: absorption of pazopanib possibly reduced by **histamine H₂-antagonists**—manufacturer of pazopanib advises give at least 2 hours before or 10 hours after histamine H₂-antagonists; absorption of pazopanib possibly reduced by **proton pump inhibitors**—manufacturer of pazopanib advises give at the same time as proton pump inhibitors

Pegfilgrastim see Filgrastim**Peginterferon Alfa** see Interferons**Pemetrexed**

Analgesics: renal excretion of pemetrexed possibly reduced by **NSAIDs** and **aspirin**—consult product literature

- Antimalarials: antifolate effect of pemetrexed increased by **pyrimethamine**
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Penicillamine

Analgesics: possible increased risk of nephrotoxicity when penicillamine given with **NSAIDs**

Penicillamine (continued)

Antacids: absorption of penicillamine reduced by **antacids**

- Antipsychotics: avoid concomitant use of penicillamine with **clozapine** (increased risk of agranulocytosis)

Cardiac Glycosides: penicillamine possibly reduces plasma concentration of **digoxin**

Gold: manufacturer of penicillamine advises avoid concomitant use with **sodium aurothiomalate** (increased risk of toxicity)

Iron: absorption of penicillamine reduced by **oral iron**

Zinc: penicillamine reduces absorption of **zinc**, also absorption of penicillamine reduced by zinc

Penicillins

Allopurinol: increased risk of rash when amoxicillin or ampicillin given with **allopurinol**

Antibacterials: absorption of phenoxymethylpenicillin reduced by **neomycin**; effects of penicillins possibly antagonised by **tetracyclines**

Anticoagulants: an interaction between broad-spectrum penicillins and **coumarins** and **phenindione** has not been demonstrated in studies, but common experience in anticoagulant clinics is that INR can be altered

- Antiepileptics: manufacturer of pivmecillinam advises avoid concomitant use with **valproate**

Cytotoxics: penicillins reduce excretion of **methotrexate** (increased risk of toxicity)

Muscle Relaxants: piperacillin enhances effects of **non-depolarising muscle relaxants** and **suxamethonium**

Mycophenolate: co-amoxiclav possibly reduces plasma concentration of **mycophenolate**

Probenecid: excretion of penicillins reduced by **probenecid** (increased plasma concentration)

Sulfinpyrazone: excretion of penicillins reduced by **sulfinpyrazone**

Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Pentamidine Isetionate

- Anti-arrhythmics: increased risk of ventricular arrhythmias when pentamidine isetionate given with **amiodarone**—avoid concomitant use; possible increased risk of ventricular arrhythmias when pentamidine isetionate given with **disopyramide**

- Antibacterials: increased risk of ventricular arrhythmias when pentamidine isetionate given with **parenteral erythromycin**; increased risk of ventricular arrhythmias when pentamidine isetionate given with **moxifloxacin**—avoid concomitant use; possible increased risk of ventricular arrhythmias when parenteral pentamidine isetionate given with **tetracycline**

- Antidepressants: avoidance of pentamidine isetionate advised by manufacturer of **citalopram** and **escitalopram** (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when pentamidine isetionate given with **tricyclics**

Antifungals: possible increased risk of nephrotoxicity when pentamidine isetionate given with **amphotericin**

- Antimalarials: avoidance of pentamidine isetionate advised by manufacturer of **piperazine** with **artemisinin** (possible risk of ventricular arrhythmias)

- Antipsychotics: increased risk of ventricular arrhythmias when pentamidine isetionate given with **amisulpride** or **droperidol**—avoid concomitant use; increased risk of ventricular arrhythmias when pentamidine isetionate given with **phenothiazines**

- Antivirals: increased risk of hypocalcaemia when parenteral pentamidine isetionate given with **foscarnet**; increased risk of ventricular arrhythmias when pentamidine isetionate given with **saquinavir**—avoid concomitant use

Pentamidine Isetionate (*continued*)

- Cytotoxics: possible increased risk of ventricular arrhythmias when pentamidine isetionate given with
 - **vandetanib**—avoid concomitant use
- Ivabradine: increased risk of ventricular arrhythmias when pentamidine isetionate given with • **ivabradine**

Pentazocine *see* Opioid Analgesics**Pentostatin**

- Antipsychotics: avoid concomitant use of cytotoxics with
 - **clozapine** (increased risk of agranulocytosis)
- Cytotoxics: increased toxicity when pentostatin given with high-dose
 - **cyclophosphamide**—avoid concomitant use; increased pulmonary toxicity when pentostatin given with • **fludarabine** (unacceptably high incidence of fatalities)

Pentoxifylline

- Analgesics: possible increased risk of bleeding when pentoxifylline given with **NSAIDs**; increased risk of bleeding when pentoxifylline given with • **ketorolac** (avoid concomitant use)

Theophylline: pentoxifylline increases plasma concentration of theophylline

Perampanel

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and • **tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by • **SSRIs** and • **tricyclics** (convulsive threshold lowered)
- Antiepileptics: plasma concentration of perampanel reduced by • **carbamazepine**, • **oxcarbazepine** and • **phenytoin** (*see* Dose under Perampanel, p. 226); plasma concentration of perampanel reduced by **topiramate**
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by • **mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by • **antipsychotics** (convulsive threshold lowered)
- Anxiolytics and Hypnotics: perampanel reduces plasma concentration of **midazolam**
- Orlistat: possible increased risk of convulsions when antiepileptics given with • **orlistat**
- Progestogens: perampanel accelerates metabolism of • **progestogens** (reduced contraceptive effect—*see* p. 402)

Pergolide

Antipsychotics: effects of pergolide antagonised by **antipsychotics**
 Memantine: effects of dopaminergics possibly enhanced by **memantine**
 Methyl dopa: antiparkinsonian effect of dopaminergics antagonised by **methyl dopa**
 Metoclopramide: antiparkinsonian effect of pergolide antagonised by **metoclopramide**

Pericyazine *see* Antipsychotics**Perindopril** *see* ACE Inhibitors**Perphenazine** *see* Antipsychotics**Pethidine** *see* Opioid Analgesics**Phenelzine** *see* MAOIs**Phenindione**

Note Change in patient's clinical condition particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect anticoagulant control

- Alcohol: anticoagulant control with phenindione may be affected by major changes in consumption of • **alcohol**
- Anabolic Steroids: anticoagulant effect of phenindione enhanced by • **anabolic steroids**
- Analgesics: anticoagulant effect of phenindione possibly enhanced by • **NSAIDs**; increased risk of haemorrhage when anticoagulants given with *intravenous* • **diclofenac** (avoid concomitant use, includ-

Phenindione**Analgesics** (*continued*)

- ing low-dose heparins); increased risk of haemorrhage when anticoagulants given with • **ketorolac** (avoid concomitant use, including low-dose heparins); increased risk of bleeding when phenindione given with • **aspirin** (due to antiplatelet effect)
- Anti-arrhythmics: metabolism of phenindione inhibited by • **amiodarone** (enhanced anticoagulant effect); anticoagulant effect of phenindione possibly enhanced by • **dronedarone**
- Antibacterials: experience in anticoagulant clinics suggests that INR possibly altered when phenindione is given with • **neomycin** (given for local action on gut); anticoagulant effect of phenindione possibly enhanced by **levofloxacin** and • **tetracyclines**; an interaction between phenindione and broad-spectrum **penicillins** has not been demonstrated in studies, but common experience in anticoagulant clinics is that INR can be altered; metabolism of phenindione possibly inhibited by **sulfonamides**
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with • **apixaban**, • **dabigatran** and • **rivaroxaban** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Antivirals: anticoagulant effect of phenindione possibly enhanced by • **ritonavir**
- Clopidogrel: anticoagulant effect of phenindione enhanced due to antiplatelet action of • **clopidogrel**
- Corticosteroids: anticoagulant effect of phenindione may be enhanced or reduced by **corticosteroids**
- Dipyridamole: anticoagulant effect of phenindione enhanced due to antiplatelet action of • **dipyridamole**
- Enteral Foods: anticoagulant effect of phenindione antagonised by vitamin K (present in some • **enteral feeds**)
- Iloprost: increased risk of bleeding when phenindione given with **iloprost**
- Lipid-regulating Drugs: anticoagulant effect of phenindione may be enhanced or reduced by • **colestyramine**; anticoagulant effect of phenindione possibly enhanced by • **rosuvastatin**; anticoagulant effect of phenindione enhanced by • **fibrates**
- Oestrogens: anticoagulant effect of phenindione antagonised by • **oestrogens**
- Prasugrel: possible increased risk of bleeding when phenindione given with **prasugrel**
- Progestogens: anticoagulant effect of phenindione antagonised by • **progestogens**
- Testolactone: anticoagulant effect of phenindione enhanced by • **testolactone**
- Testosterone: anticoagulant effect of phenindione enhanced by • **testosterone**
- Thyroid Hormones: anticoagulant effect of phenindione enhanced by • **thyroid hormones**
- Vitamins: anticoagulant effect of phenindione antagonised by • **vitamin K**

Phenobarbital

Note Primidone interactions as for phenobarbital

Alcohol: increased sedative effect when phenobarbital given with **alcohol**

Analgesics: phenobarbital reduces plasma concentration of **methadone**; phenobarbital possibly accelerates metabolism of **paracetamol** (also isolated reports of hepatotoxicity)

- Anti-arrhythmics: phenobarbital accelerates metabolism of **disopyramide** (reduced plasma concentration); phenobarbital possibly reduces plasma concentration of • **dronedarone**—avoid concomitant use; phenobarbital possibly accelerates metabolism of **propafenone**
- Antibacterials: phenobarbital accelerates metabolism of **metronidazole** (reduced effect); phenobarbital possibly reduces plasma concentration of **rif-**

Phenobarbital

- **Antibacterials** (*continued*)
 - **ampicillin**; phenobarbital accelerates metabolism of **doxycycline** (reduced plasma concentration); phenobarbital possibly accelerates metabolism of **chloramphenicol** (reduced plasma concentration); phenobarbital reduces plasma concentration of **tetracycline** (avoid during and for 2 weeks after phenobarbital)
- **Anticoagulants**: phenobarbital accelerates metabolism of **coumarins** (reduced anticoagulant effect); phenobarbital possibly reduces plasma concentration of **rivaroxaban**—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- **Antidepressants**: phenobarbital possibly reduces plasma concentration of **reboxetine**; phenobarbital reduces plasma concentration of **paroxetine**; phenobarbital accelerates metabolism of **mianserin** (reduced plasma concentration); anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIs** and **tricyclics** (convulsive threshold lowered); plasma concentration of phenobarbital possibly reduced by **St John's wort**—avoid concomitant use; phenobarbital possibly accelerates metabolism of **tricyclics** (reduced plasma concentration)
- **Antiepileptics**: plasma concentration of phenobarbital possibly increased by **carbamazepine**; phenobarbital possibly reduces plasma concentration of **ethosuximide**, **rufinamide** and **topiramate**; phenobarbital reduces plasma concentration of **lamotrigine**, **tiagabine** and **zonisamide**; plasma concentration of phenobarbital increased by **oxcarbazepine**, also plasma concentration of an active metabolite of oxcarbazepine reduced; plasma concentration of phenobarbital often increased by **phenytoin**, plasma concentration of phenytoin often reduced but may be increased; plasma concentration of phenobarbital increased by **stiripentol**; plasma concentration of phenobarbital increased by **valproate** (also plasma concentration of valproate reduced)
- **Antifungals**: phenobarbital possibly reduces plasma concentration of **itraconazole** and **posaconazole**; phenobarbital possibly reduces plasma concentration of **voriconazole**—avoid concomitant use; phenobarbital reduces absorption of **griseofulvin** (reduced effect)
- **Antimalarials**: avoidance of phenobarbital advised by manufacturer of **piperazine with arteminol**; anticonvulsant effect of antiepileptics antagonised by **mefloquine**
- **Antipsychotics**: anticonvulsant effect of antiepileptics antagonised by **antipsychotics** (convulsive threshold lowered); phenobarbital accelerates metabolism of **haloperidol** (reduced plasma concentration); plasma concentration of both drugs reduced when phenobarbital given with **chlorpromazine**; phenobarbital possibly reduces plasma concentration of **aripiprazole** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); phenobarbital possibly reduces plasma concentration of **clozapine**
- **Antivirals**: phenobarbital possibly reduces plasma concentration of **abacavir**, **darunavir**, **fosamprenavir**, **indinavir**, **lopinavir** and **sacquinavir**; avoidance of phenobarbital advised by manufacturer of **boceprevir** and **rilpivirine** (plasma concentration of boceprevir and rilpivirine possibly reduced); avoidance of phenobarbital advised by manufacturer of **dolutegravir**, **elvitegravir**, **etravirine**, **sofosbuvir** and **telaprevir**

Anxiolytics and Hypnotics: increased sedative effect when phenobarbital given with **anxiolytics and hyp-**

Phenobarbital

Anxiolytics and Hypnotics (*continued*)

- **notics**; phenobarbital often reduces plasma concentration of **clonazepam**
- **Aprepitant**: phenobarbital possibly reduces plasma concentration of **aprepitant**
- **Beta-blockers**: phenobarbital possibly reduces plasma concentration of **propranolol**
- **Caffeine citrate**: effects of phenobarbital possibly antagonised by **caffeine citrate**
- **Calcium-channel Blockers**: phenobarbital probably reduces effects of **calcium-channel blockers**; avoidance of phenobarbital advised by manufacturer of **nimodipine** (plasma concentration of nimodipine reduced)
- **Ciclosporin**: phenobarbital accelerates metabolism of **ciclosporin** (reduced plasma concentration)
- **Cobicistat**: phenobarbital possibly reduces plasma concentration of **cobicistat**—manufacturer of cobicistat advises avoid concomitant use
- **Corticosteroids**: phenobarbital accelerates metabolism of **corticosteroids** (reduced effect)
- **Cytotoxics**: phenobarbital possibly decreases plasma concentration of **axitinib** (increase dose of axitinib—consult axitinib product literature); phenobarbital possibly reduces plasma concentration of **bosutinib** and **crizotinib**—manufacturer of bosutinib and crizotinib advises avoid concomitant use; avoidance of phenobarbital advised by manufacturer of **cabazitaxel**, **dabrafenib** and **gefitinib**; avoidance of phenobarbital advised by manufacturer of **vandetanib** (plasma concentration of vandetanib possibly reduced); phenobarbital possibly reduces plasma concentration of **etoposide**; phenobarbital reduces plasma concentration of **irinotecan** and its active metabolite; manufacturer of procarbazine advises possible increased risk of hypersensitivity reactions when phenobarbital given with **procarbazine**
- **Diuretics**: phenobarbital reduces plasma concentration of **furosemide**—avoid concomitant use; increased risk of osteomalacia when phenobarbital given with **carbonic anhydrase inhibitors**
- **Folates**: plasma concentration of phenobarbital possibly reduced by **folates**
- **Hormone Antagonists**: phenobarbital possibly reduces plasma concentration of **abiraterone**—manufacturer of abiraterone advises avoid concomitant use; phenobarbital accelerates metabolism of **toremifene** (reduced plasma concentration)
- **Ivacaftor**: phenobarbital possibly reduces plasma concentration of **ivacaftor**—manufacturer of ivacaftor advises avoid concomitant use
- **Leukotriene Receptor Antagonists**: phenobarbital reduces plasma concentration of **montelukast**
- **Oestrogens**: phenobarbital accelerates metabolism of **oestrogens** (reduced contraceptive effect—see p. 402)
- **Orlistat**: possible increased risk of convulsions when antiepileptics given with **orlistat**
- **Progestogens**: phenobarbital accelerates metabolism of **progestogens** (reduced contraceptive effect—see p. 402)
- **Roflumilast**: phenobarbital possibly inhibits effects of **roflumilast** (manufacturer of roflumilast advises avoid concomitant use)
- **Sodium Oxybate**: avoidance of phenobarbital advised by manufacturer of **sodium oxybate**
- **Sympathomimetics**: plasma concentration of phenobarbital possibly increased by **methylphenidate**
- **Tacrolimus**: phenobarbital reduces plasma concentration of **tacrolimus**
- **Theophylline**: phenobarbital accelerates metabolism of **theophylline** (reduced effect)

Phenobarbital (*continued*)

Thyroid Hormones: phenobarbital accelerates metabolism of **thyroid hormones** (may increase requirements for thyroid hormones in hypothyroidism)

Ticagrelor: phenobarbital possibly reduces plasma concentration of **ticagrelor**

- Ullipristal: avoidance of phenobarbital advised by manufacturer of **•ullipristal** (contraceptive effect of ullipristal possibly reduced)

Vitamins: phenobarbital possibly increases requirements for **vitamin D**

Phenothiazines *see* Antipsychotics**Phenoxybenzamine** *see* Alpha-blockers**Phenoxymethylpenicillin** *see* Penicillins**Phentolamine** *see* Alpha-blockers**Phenylephrine** *see* Sympathomimetics**Phenytoin**

Note Fosphenytoin interactions as for phenytoin

Alcohol: plasma concentration of phenytoin possibly reduced by chronic heavy consumption of **alcohol**

- Analgesics: excretion of phenytoin possibly reduced by **•acetamin** (increased risk of toxicity); phenytoin possibly accelerates metabolism of **•fentanyl** (reduced effect); phenytoin accelerates metabolism of **•methadone** (reduced effect and risk of withdrawal effects); phenytoin possibly increases risk of **•pethidine** toxicity; effects of phenytoin enhanced by **•aspirin**; phenytoin possibly accelerates metabolism of **•paracetamol** (also isolated reports of hepatotoxicity)

Antacids: absorption of phenytoin reduced by **antacids**

- Anti-arrhythmics: metabolism of phenytoin inhibited by **•amiodarone** (increased plasma concentration); phenytoin reduces plasma concentration of **•disopyramide**; phenytoin possibly reduces plasma concentration of **•dronedrone**—avoid concomitant use
- Antibacterials: metabolism of phenytoin inhibited by **•clarithromycin** (increased plasma concentration); metabolism of phenytoin possibly inhibited by **•metronidazole** (increased plasma concentration); plasma concentration of phenytoin increased or decreased by **•ciprofloxacin**; phenytoin accelerates metabolism of **•doxycycline** (reduced plasma concentration); plasma concentration of phenytoin increased by **•chloramphenicol** (increased risk of toxicity); metabolism of phenytoin possibly inhibited by **•isoniazid** (increased risk of toxicity); metabolism of phenytoin accelerated by **•rifamycins** (reduced plasma concentration); plasma concentration of phenytoin possibly increased by **•sulfonamides**; phenytoin reduces plasma concentration of **•telithromycin** (avoid during and for 2 weeks after phenytoin); plasma concentration of phenytoin increased by **•trimethoprim** (also increased antifolate effect)
- Anticoagulants: phenytoin accelerates metabolism of **•coumarins** (possibility of reduced anticoagulant effect, but enhancement also reported); phenytoin possibly reduces plasma concentration of **•dabigatran**—manufacturer of dabigatran advises avoid concomitant use; phenytoin possibly reduces plasma concentration of **•rivaroxaban**—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antidepressants: plasma concentration of phenytoin increased by **•fluoxetine** and **•fluvoxamine**; phenytoin reduces plasma concentration of **•mianserin**, **•mirtazapine** and **•paroxetine**; plasma concentration of phenytoin possibly increased by **•sertraline**, also plasma concentration of sertraline possibly reduced; anticonvulsant effect of antiepileptics possibly antagonised by **•MAOIs** and **•tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **•SSRIs** and **•tricyclics** (convulsive threshold low-

Phenytoin• Antidepressants (*continued*)

ered); plasma concentration of phenytoin possibly reduced by **•St John's wort**—avoid concomitant use; phenytoin possibly reduces plasma concentration of **•tricyclics**

Antidiabetics: plasma concentration of phenytoin transiently increased by **•tolbutamide** (possibility of toxicity)

- Antiepileptics: plasma concentration of both drugs often reduced when phenytoin given with **•carbamazepine**, also plasma concentration of phenytoin may be increased; phenytoin reduces plasma concentration of **•eslicarbazine**, also plasma concentration of phenytoin increased; plasma concentration of phenytoin possibly increased by **•ethosuximide**, also plasma concentration of ethosuximide possibly reduced; phenytoin reduces plasma concentration of **•lamotrigine**, **•tiagabine** and **•zonisamide**; plasma concentration of phenytoin increased by **•oxcarbazepine**, also plasma concentration of an active metabolite of oxcarbazepine reduced; phenytoin reduces plasma concentration of **•perampanel** (see Dose under Perampanel, p. 226); phenytoin often increases plasma concentration of **•phenobarbital**, plasma concentration of phenytoin often reduced but may be increased; phenytoin possibly reduces plasma concentration of **•retigabine**; phenytoin possibly reduces plasma concentration of **•rufinamide**, also plasma concentration of phenytoin possibly increased; plasma concentration of phenytoin increased by **•stiripentol**; plasma concentration of phenytoin increased by **•topiramate** (also plasma concentration of topiramate reduced); plasma concentration of phenytoin increased or possibly reduced when given with **•valproate**, also plasma concentration of valproate reduced; plasma concentration of phenytoin reduced by **•vigabatrin**
- Antifungals: anticonvulsant effect of phenytoin enhanced by **•miconazole** (plasma concentration of phenytoin increased); plasma concentration of phenytoin increased by **•fluconazole** (consider reducing dose of phenytoin); phenytoin reduces plasma concentration of **•itraconazole**—avoid concomitant use; phenytoin reduces plasma concentration of **•posaconazole**; plasma concentration of phenytoin increased by **•voriconazole**, also phenytoin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for phenytoin toxicity); phenytoin possibly reduces plasma concentration of **•caspofungin**—consider increasing dose of caspofungin
- Antimalarials: avoidance of phenytoin advised by manufacturer of **•piperazine with arteminol**; anticonvulsant effect of antiepileptics antagonised by **•mefloquine**; anticonvulsant effect of phenytoin antagonised by **•pyrimethamine**, also increased antifolate effect
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **•antipsychotics** (convulsive threshold lowered); phenytoin reduces plasma concentration of **•haloperidol**; plasma concentration of phenytoin possibly increased or decreased by **•chlorpromazine**; phenytoin possibly reduces plasma concentration of **•aripiprazole** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); phenytoin accelerates metabolism of **•clozapine** and **•quetiapine** (reduced plasma concentration)
- Antivirals: phenytoin possibly reduces plasma concentration of **•abacavir**, **•darunavir**, **•lopinavir** and **•saquinavir**; avoidance of phenytoin advised by manufacturer of **•boceprevir** and **•rilpivirine** (plasma concentration of boceprevir and rilpivirine possibly reduced); avoidance of phenytoin advised by manu-

Phenytoin

- Antivirals (*continued*)
 - factor of **dolutegravir**, **elvitegravir**, **etravirine**, **sofosbuvir** and **telaprevir**; phenytoin possibly reduces plasma concentration of **indinavir**, also plasma concentration of phenytoin possibly increased; phenytoin possibly reduces plasma concentration of **ritonavir**, also plasma concentration of phenytoin possibly affected; plasma concentration of phenytoin increased or decreased by **zidovudine**
- Anxiolytics and Hypnotics: phenytoin often reduces plasma concentration of **clonazepam**; plasma concentration of phenytoin increased or decreased by **diazepam**; plasma concentration of phenytoin possibly increased or decreased by **benzodiazepines**
- Antiemetic: phenytoin possibly reduces plasma concentration of **aprepitant**
- Bupropion: phenytoin reduces plasma concentration of **bupropion**
- Caffeine citrate: phenytoin reduces plasma concentration of **caffeine citrate**
- Calcium-channel Blockers: phenytoin reduces effects of **felodipine** and **verapamil**; avoidance of phenytoin advised by manufacturer of **nimodipine** (plasma concentration of nimodipine possibly reduced); plasma concentration of phenytoin increased by **diltiazem** but also effect of diltiazem reduced
- Cardiac Glycosides: phenytoin possibly reduces plasma concentration of **digoxin**
- Ciclosporin: phenytoin accelerates metabolism of **ciclosporin** (reduced plasma concentration)
- Cobicistat: phenytoin possibly reduces plasma concentration of **cobicistat**—manufacturer of cobicistat advises avoid concomitant use
- Corticosteroids: phenytoin accelerates metabolism of **corticosteroids** (reduced effect)
- Cytotoxics: phenytoin possibly reduces plasma concentration of **busulfan**, **eribulin** and **etoposide**; metabolism of phenytoin possibly inhibited by **fluorouracil** (increased risk of toxicity); phenytoin increases antifolate effect of **methotrexate**; plasma concentration of phenytoin possibly reduced by **cisplatin**; phenytoin possibly decreases plasma concentration of **axitinib** (increase dose of axitinib—consult axitinib product literature); phenytoin possibly reduces plasma concentration of **bosutinib** and **crizotinib**—manufacturer of bosutinib and crizotinib advises avoid concomitant use; avoidance of phenytoin advised by manufacturer of **cabazitaxel**, **dabrafenib**, **gefitinib**, **lapatinib** and **vemurafenib**; phenytoin reduces plasma concentration of **imatinib**—avoid concomitant use; phenytoin reduces plasma concentration of **irinotecan** and its active metabolite; manufacturer of procarbazine advises possible increased risk of hypersensitivity reactions when phenytoin given with **procarbazine**; avoidance of phenytoin advised by manufacturer of **vismodegib** (plasma concentration of vismodegib possibly reduced)
- Diazoxide: plasma concentration of phenytoin reduced by **diazoxide**, also effect of diazoxide may be reduced
- Disulfiram: metabolism of phenytoin inhibited by **disulfiram** (increased risk of toxicity)
- Diuretics: plasma concentration of phenytoin possibly increased by **acetazolamide**; phenytoin antagonises effects of **furosemide**; phenytoin reduces plasma concentration of **eplerenone**—avoid concomitant use; increased risk of osteomalacia when phenytoin given with **carbonic anhydrase inhibitors**
- Dopaminergics: phenytoin possibly reduces effects of **levodopa**
- Enteral Foods: absorption of phenytoin possibly reduced by **enteral feeds**
- Folates: plasma concentration of phenytoin possibly reduced by **folates**

Phenytoin (*continued*)

- Hormone Antagonists: phenytoin possibly reduces plasma concentration of **abiraterone**—manufacturer of abiraterone advises avoid concomitant use; phenytoin possibly accelerates metabolism of **toremifene**
 - 5HT₂-receptor Antagonists: phenytoin accelerates metabolism of **ondansetron** (reduced effect)
 - Ivacaftor: phenytoin possibly reduces plasma concentration of **ivacaftor**—manufacturer of ivacaftor advises avoid concomitant use
 - Leflunomide: plasma concentration of phenytoin possibly increased by **leflunomide**
 - Levamisole: plasma concentration of phenytoin possibly increased by **levamisole**
 - Lipid-regulating Drugs: absorption of phenytoin possibly reduced by **colessevelam**; combination of phenytoin with **fluvastatin** may increase plasma concentration of either drug (or both)
 - Lithium: neurotoxicity may occur when phenytoin given with **lithium** without increased plasma concentration of lithium
 - Macitentan: avoidance of phenytoin advised by manufacturer of **macitentan**
 - Modafinil: plasma concentration of phenytoin possibly increased by **modafinil**
 - Muscle Relaxants: *long-term use* of phenytoin reduces effects of **non-depolarising muscle relaxants** (but *acute use* of phenytoin might increase effects of non-depolarising muscle relaxants)
 - Oestrogens: phenytoin accelerates metabolism of **oestrogens** (reduced contraceptive effect—see p. 402)
 - Orlistat: possible increased risk of convulsions when antiepileptics given with **orlistat**
 - Progestogens: phenytoin accelerates metabolism of **progestogens** (reduced contraceptive effect—see p. 402)
 - Roflumilast: phenytoin possibly inhibits effects of **roflumilast** (manufacturer of roflumilast advises avoid concomitant use)
 - Sulfinpyrazone: plasma concentration of phenytoin increased by **sulfinpyrazone**
 - Sympathomimetics: plasma concentration of phenytoin increased by **methylphenidate**
 - Tacrolimus: phenytoin reduces plasma concentration of **tacrolimus**, also plasma concentration of phenytoin possibly increased
 - Theophylline: plasma concentration of both drugs reduced when phenytoin given with **theophylline**
 - Thyroid Hormones: phenytoin accelerates metabolism of **thyroid hormones** (may increase requirements in hypothyroidism), also plasma concentration of phenytoin possibly increased
 - Tibolone: phenytoin accelerates metabolism of **tibolone**
 - Ticagrelor: phenytoin possibly reduces plasma concentration of **ticagrelor**
 - Ulcer-healing Drugs: metabolism of phenytoin inhibited by **cimetidine** (increased plasma concentration); effects of phenytoin enhanced by **esomeprazole**; effects of phenytoin possibly enhanced by **omeprazole**; absorption of phenytoin reduced by **sucralfate**
 - Ulipristal: avoidance of phenytoin advised by manufacturer of **ulipristal** (contraceptive effect of ulipristal possibly reduced)
 - Vaccines: effects of phenytoin enhanced by **influenza vaccine**
 - Vitamins: phenytoin possibly increases requirements for **vitamin D**
- Pholcodine**
- Antidepressants: manufacturer of pholcodine advises avoid for 2 weeks after stopping **MAOIs**

Phosphodiesterase Type-3 Inhibitors

- Anagrelide: avoidance of enoximone and milrinone advised by manufacturer of ● **anagrelide**

Physostigmine *see* Parasympathomimetics**Pilocarpine** *see* Parasympathomimetics**Pimozide** *see* Antipsychotics**Pindolol** *see* Beta-blockers**Pioglitazone** *see* Antidiabetics**Piperacillin** *see* Penicillins**Piperaquine** *see* Piperaquine with Arteminol**Piperaquine with Arteminol**

Note Piperaquine has a long half-life; there is a potential for drug interactions to occur for up to 3 months after treatment has been stopped

- Analgesics: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **methadone** (possible risk of ventricular arrhythmias)
- Anti-arrhythmics: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **amiodarone** and ● **disopyramide** (possible risk of ventricular arrhythmias)
- Antibacterials: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **macrolides** and ● **moxifloxacin** (possible risk of ventricular arrhythmias); manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **rifampicin**
- Antidepressants: avoidance of antimalarials advised by manufacturer of ● **citalopram** and ● **escitalopram** (risk of ventricular arrhythmias); manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **antidepressants**

Antiepileptics: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **carbamazepine**, ● **phenobarbital** and ● **phenytoin**

- Antifungals: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **imidazoles** and ● **triazoles** (possible risk of ventricular arrhythmias)
 - Antihistamines: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **mizolastine** (possible risk of ventricular arrhythmias)
 - Antimalarials: avoidance of antimalarials advised by manufacturer of ● **artemether with lumefantrine**
 - Antipsychotics: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **droperidol**, ● **haloperidol**, ● **phenothiazines** and ● **pimozide** (possible risk of ventricular arrhythmias)
 - Antivirals: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **saquinavir** (possible risk of ventricular arrhythmias)
 - Beta-blockers: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **sotalol** (possible risk of ventricular arrhythmias)
 - Cytotoxics: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **arsenic trioxide** (possible risk of ventricular arrhythmias); manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **vinblastine**, ● **vincristine**, ● **vinflunine** and ● **vinorelbine**
 - Domperidone: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **domperidone** (possible risk of ventricular arrhythmias)
- Grapefruit Juice: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **grapefruit juice**
- Histamine: avoidance of antimalarials advised by manufacturer of ● **histamine**
- Pentamidine Isetionate: manufacturer of piperaquine with arteminol advises avoid concomitant use with ● **pentamidine isetionate** (possible risk of ventricular arrhythmias)
- Vaccines: antimalarials inactivate ● **oral typhoid vaccine**—see p. 626

Piprotiazine *see* Antipsychotics**Pirfenidone**

- Antibacterials: plasma concentration of pirfenidone increased by ● **ciprofloxacin**—see Cautions under Pirfenidone, BNf section 3.11
 - Antidepressants: plasma concentration of pirfenidone increased by ● **fluvoxamine**—manufacturer of pirfenidone advises avoid concomitant use
- Grapefruit Juice: manufacturer of pirfenidone advises avoid concomitant use with ● **grapefruit juice**

Piroxicam *see* NSAIDs**Pivmecillinam** *see* Penicillins**Pixantrone**

- Antipsychotics: avoid concomitant use of cytotoxics with ● **clozapine** (increased risk of agranulocytosis)
- Vaccines: avoid concomitant use of pixantrone with live ● **vaccines** (see p. 604)

Pizotifen

Adrenergic Neurone Blockers: pizotifen antagonises hypotensive effect of ● **adrenergic neurone blockers**

Platinum Compounds

- Aldesleukin: avoidance of cisplatin advised by manufacturer of ● **aldesleukin**
 - Antibacterials: increased risk of nephrotoxicity and possibly of ototoxicity when platinum compounds given with ● **aminoglycosides** or ● **polymyxins**; increased risk of nephrotoxicity and ototoxicity when platinum compounds given with ● **capreomycin**; increased risk of nephrotoxicity and possibly of ototoxicity when cisplatin given with ● **vancomycin**
- Antiepileptics: cisplatin possibly reduces plasma concentration of ● **phenytoin**

- Antipsychotics: avoid concomitant use of cytotoxics with ● **clozapine** (increased risk of agranulocytosis)
- Cytotoxics: increased risk of toxicity when cisplatin given with ● **ifosfamide**; increased pulmonary toxicity when cisplatin given with ● **bleomycin** and ● **methotrexate**

Diuretics: increased risk of nephrotoxicity and ototoxicity when platinum compounds given with ● **diuretics**

Polymyxin B *see* Polymyxins**Polymyxins**

- Antibacterials: increased risk of nephrotoxicity when colistimethate sodium or polymyxins given with ● **aminoglycosides**; increased risk of nephrotoxicity when colistimethate sodium or polymyxins given with ● **capreomycin**; increased risk of nephrotoxicity when polymyxins given with ● **vancomycin**; increased risk of nephrotoxicity and ototoxicity when colistimethate sodium given with ● **vancomycin**
- Antifungals: increased risk of nephrotoxicity when polymyxins given with ● **amphotericin**
- Ciclosporin: increased risk of nephrotoxicity when polymyxins given with ● **ciclosporin**
 - Cytotoxics: increased risk of nephrotoxicity and possibly of ototoxicity when polymyxins given with ● **platinum compounds**
 - Diuretics: increased risk of toxicity when polymyxins given with ● **loop diuretics**
 - Muscle Relaxants: polymyxins enhance effects of ● **non-depolarising muscle relaxants** and ● **suxamethonium**
 - Parasympathomimetics: polymyxins antagonise effects of ● **neostigmine** and ● **pyridostigmine**
- Vaccines: antibacterials inactivate ● **oral typhoid vaccine**—see p. 626

Polystyrene Sulfonate Resins

Antacids: risk of intestinal obstruction when polystyrene sulfonate resins given with ● **aluminium hydroxide**; risk of metabolic alkalosis when polystyrene sulfonate resins given with ● **oral magnesium salts**

Thyroid Hormones: polystyrene sulfonate resins reduce absorption of ● **levothyroxine**

Pomalidomide

- Antidepressants: plasma concentration of pomalidomide increased by ● **fluvoxamine**

Progestogens (*continued*)

- Anticoagulants: progestogens may enhance or reduce anticoagulant effect of **coumarins**; progestogens antagonise anticoagulant effect of **phenindione**
- Antidepressants: contraceptive effect of progestogens reduced by **St John's wort** (avoid concomitant use)

Antidiabetics: progestogens antagonise hypoglycaemic effect of **antidiabetics**

- Antiepileptics: metabolism of progestogens accelerated by **carbamazepine**, **eslicarbazepine**, **oxcarbazepine**, **perampanel**, **phenobarbital**, **phenytoin**, **rufinamide** and **topiramate** (reduced contraceptive effect—see p. 402); desogestrel possibly increases plasma concentration of **lamotrigine**

Antifungals: progestogens possibly increase plasma concentration of **voriconazole**; anecdotal reports of contraceptive failure and menstrual irregularities when progestogens given with **griseofulvin**; occasional reports of breakthrough bleeding when progestogens (used for contraception) given with **terbinafine**

- Antivirals: plasma concentration of norethisterone increased by **atazanavir**; plasma concentration of drospirenone increased by **boceprevir** (increased risk of toxicity); contraceptive effect of progestogens possibly reduced by **efavirenz**; plasma concentration of norgestimate increased by **elvitegravir**; metabolism of progestogens accelerated by **nevirapine** (reduced contraceptive effect—see p. 402)

Anxiolytics and Hypnotics: progestogens possibly increase plasma concentration of **chlordiazepoxide**, **diazepam** and **nitrazepam**; progestogens possibly reduce plasma concentration of **lorazepam**, **oxazepam** and **temazepam**

- Appetit: possible contraceptive failure of hormonal contraceptives containing progestogens when given with **aprepitant** (alternative contraception recommended)
- Bosentan: possible contraceptive failure of hormonal contraceptives containing progestogens when given with **bosentan** (alternative contraception recommended)

Ciclosporin: progestogens possibly increase plasma concentration of **ciclosporin**

Cobicistat: plasma concentration of norgestimate increased by **cobicistat**

- Cytotoxics: possible reduction in contraceptive effect of progestogens advised by manufacturer of **crizotinib** and **vemurafenib**; possible reduced contraceptive effect of hormonal contraceptives containing progestogens advised by manufacturer of **dabrafenib** (alternative contraception recommended)

Diuretics: risk of hyperkalaemia when drospirenone given with **potassium-sparing diuretics** and **aldosterone antagonists** (monitor serum potassium during first cycle)

- Dopaminergics: progestogens increase plasma concentration of **selegiline**—manufacturer of selegiline advises avoid concomitant use

Lipid-regulating Drugs: plasma concentration of norethisterone increased by **atorvastatin**; plasma concentration of active metabolite of norgestimate increased by **rosuvastatin**; plasma concentration of norgestrel increased by **rosuvastatin**

Muscle Relaxants: progestogens possibly increase plasma concentration of **tizanidine** (increased risk of toxicity)

Sugammadex: plasma concentration of progestogens possibly reduced by **sugammadex**—manufacturer of sugammadex advises additional contraceptive precautions

Terflunomide: plasma concentration of levonorgestrel increased by **terflunomide**

Progestogens (*continued*)

- Ulipristal: contraceptive effect of progestogens possibly reduced by **ulipristal**

Proguanil

Antacids: absorption of proguanil reduced by **oral magnesium salts** (as magnesium trisilicate)

Anticoagulants: isolated reports that proguanil may enhance anticoagulant effect of **warfarin**

- Antidepressants: avoidance of antimalarials advised by manufacturer of **escitalopram** and **escitalopram** (risk of ventricular arrhythmias)

- Antimalarials: avoidance of antimalarials advised by manufacturer of **artemether with lumefantrine**; increased antifolate effect when proguanil given with **pyrimethamine**

Antivirals: plasma concentration of proguanil possibly affected by **efavirenz**

Histamine: avoidance of antimalarials advised by manufacturer of **histamine**

Vaccines: antimalarials inactivate **oral typhoid vaccine**—see p. 626

Promazine *see* Antipsychotics

Promethazine *see* Antihistamines

Propafenone

Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with **bupivacaine**, **levobupivacaine**, **prilocaine** or **ropivacaine**

- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other **anti-arrhythmics**

- Antibacterials: metabolism of propafenone accelerated by **rifampicin** (reduced effect)

- Anticoagulants: propafenone enhances anticoagulant effect of **coumarins**

- Antidepressants: metabolism of propafenone possibly inhibited by **fluoxetine** and **paroxetine**; increased risk of arrhythmias when propafenone given with **tricyclics**

Antiepileptics: metabolism of propafenone possibly accelerated by **phenobarbital**

Antihistamines: avoidance of propafenone advised by manufacturer of **mizolastine** (possible risk of ventricular arrhythmias)

- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with **antipsychotics** that prolong the QT interval

- Antivirals: plasma concentration of propafenone possibly increased by **fosamprenavir** (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of propafenone increased by **ritonavir** (increased risk of ventricular arrhythmias—avoid concomitant use); increased risk of ventricular arrhythmias when propafenone given with **saqueinavir**—avoid concomitant use; caution with propafenone advised by manufacturer of **telaprevir** (risk of ventricular arrhythmias)

- Beta-blockers: increased myocardial depression when anti-arrhythmics given with **beta-blockers**; propafenone increases plasma concentration of **metoprolol** and **propranolol**

- Cardiac Glycosides: propafenone increases plasma concentration of **digoxin** (halve dose of digoxin)

Ciclosporin: propafenone possibly increases plasma concentration of **ciclosporin**

Parasympathomimetics: propafenone possibly antagonises effects of **neostigmine** and **pyridostigmine**

Theophylline: propafenone increases plasma concentration of **theophylline**

- Ulcer-healing Drugs: plasma concentration of propafenone increased by **cimetidine**

Propantheline *see* Antimuscarinics

Propiverine *see* Antimuscarinics

Propofol *see* Anaesthetics, General

Propranolol *see* Beta-blockers

Prostaglandins

- ACE Inhibitors: enhanced hypotensive effect when alprostadil given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when alprostadil given with **adrenergic neurone blockers**
- Alpha-blockers: enhanced hypotensive effect when alprostadil given with **alpha-blockers**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when alprostadil given with **angiotensin-II receptor antagonists**
- Beta-blockers: enhanced hypotensive effect when alprostadil given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when alprostadil given with **calcium-channel blockers**
- Clonidine: enhanced hypotensive effect when alprostadil given with **clonidine**
- Diazoxide: enhanced hypotensive effect when alprostadil given with **diazoxide**
- Diuretics: enhanced hypotensive effect when alprostadil given with **diuretics**
- Methyldopa: enhanced hypotensive effect when alprostadil given with **methyldopa**
- Moxonidine: enhanced hypotensive effect when alprostadil given with **moxonidine**
- Nitrates: enhanced hypotensive effect when alprostadil given with **nitrates**
- Oxytocin: prostaglandins potentiate uterotonic effect of **oxytocin**
- Vasodilator Antihypertensives: enhanced hypotensive effect when alprostadil given with **hydralazine**, **minoxidil** or **sodium nitroprusside**

Protein Kinase Inhibitors *see* individual drugs

Proton Pump Inhibitors

- Antacids: absorption of lansoprazole possibly reduced by **antacids**
- Antibacterials: plasma concentration of both drugs increased when omeprazole given with **clarithromycin**
- Anticoagulants: esomeprazole and omeprazole possibly enhance anticoagulant effect of **coumarins**; pantoprazole might enhance the anticoagulant effect of **coumarins**
- Antidepressants: omeprazole increases plasma concentration of **escitalopram**; plasma concentration of lansoprazole possibly increased by **fluvoxamine**; plasma concentration of omeprazole possibly reduced by **St John's wort**
- Antiepileptics: omeprazole possibly enhances effects of **phenytoin**; esomeprazole enhances effects of **phenytoin**
- Antifungals: proton pump inhibitors reduce absorption of **itraconazole**; avoidance of proton pump inhibitors advised by manufacturer of **posaconazole** (plasma concentration of posaconazole possibly reduced); plasma concentration of esomeprazole possibly increased by **voriconazole**; plasma concentration of omeprazole increased by **voriconazole** (consider reducing dose of omeprazole)
- Antipsychotics: omeprazole possibly reduces plasma concentration of **clozapine**
- Antivirals: proton pump inhibitors reduce plasma concentration of **atazanavir**—avoid or adjust dose of both drugs (consult product literature); omeprazole increases plasma concentration of **raltegravir**; avoidance of esomeprazole, lansoprazole, pantoprazole and rabeprazole advised by manufacturer of **rilpivirine** (plasma concentration of rilpivirine possibly reduced); omeprazole reduces plasma concentration of **rilpivirine**—avoid concomitant use; esomeprazole, lansoprazole, pantoprazole and rabeprazole possibly increase plasma concentration of **saquinavir**—manufacturer of saquinavir advises avoid concomitant use; omeprazole increases plasma concentration of **saquinavir**—manufacturer of saquinavir

Proton Pump Inhibitors

- Antivirals (*continued*)
 - advises avoid concomitant use; plasma concentration of esomeprazole and omeprazole reduced by **tipranavir**
- Anxiolytics and Hypnotics: esomeprazole and omeprazole possibly inhibit metabolism of **diazepam** (increased plasma concentration)
- Cardiac Glycosides: proton pump inhibitors possibly slightly increase plasma concentration of **digoxin**
- Ciclosporin: omeprazole possibly affects plasma concentration of **ciclosporin**
- Cilostazol: omeprazole increases plasma concentrations of **cilostazol** (see Dose under Cilostazol, BNF section 2.6.4)
- Clopidogrel: esomeprazole and omeprazole reduce antiplatelet effect of **clopidogrel**; lansoprazole, pantoprazole and rabeprazole possibly reduce antiplatelet effect of **clopidogrel**
- Cytotoxics: proton pump inhibitors possibly reduce excretion of **methotrexate** (increased risk of toxicity); lansoprazole reduces plasma concentration of **bosutinib**; avoidance of proton pump inhibitors advised by manufacturer of **dabrafenib** (plasma concentration of dabrafenib possibly reduced); avoidance of esomeprazole, lansoprazole, pantoprazole and rabeprazole advised by manufacturer of **erlotinib**; omeprazole reduces plasma concentration of **erlotinib**—manufacturer of erlotinib advises avoid concomitant use; proton pump inhibitors possibly reduce absorption of **lapatinib**; proton pump inhibitors possibly reduce absorption of **pazopanib**—manufacturer of pazopanib advises give at the same time as proton pump inhibitors
- Tacrolimus: omeprazole possibly increases plasma concentration of **tacrolimus**
- Ulcer-healing Drugs: absorption of lansoprazole possibly reduced by **sucralfate**
- Ulipristal: avoidance of proton pump inhibitors advised by manufacturer of **high-dose ulipristal** (contraceptive effect of ulipristal possibly reduced)

Pseudoephedrine *see* Sympathomimetics

Pyrazinamide

- Probenecid: pyrazinamide antagonises effects of **probenecid**
- Sulfinpyrazone: pyrazinamide antagonises effects of **sulfinpyrazone**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Pyridostigmine *see* Parasympathomimetics

Pyridoxine *see* Vitamins

Pyrimethamine

- Antibacterials: increased antifolate effect when pyrimethamine given with **sulfonamides** or **trimethoprim**
- Antidepressants: avoidance of antimalarials advised by manufacturer of **escitalopram** and **escitalopram** (risk of ventricular arrhythmias)
- Antiepileptics: pyrimethamine antagonises anti-convulsant effect of **phenytoin**, also increased antifolate effect
- Antimalarials: avoidance of antimalarials advised by manufacturer of **artemether with lumefantrine**; increased antifolate effect when pyrimethamine given with **proguanil**
- Antivirals: increased antifolate effect when pyrimethamine given with **zidovudine**
- Cytotoxics: pyrimethamine increases antifolate effect of **methotrexate** and **pemetrexed**
- Histamine: avoidance of antimalarials advised by manufacturer of **histamine**
- Vaccines: antimalarials inactivate **oral typhoid vaccine**—*see* p. 626

Quetiapine *see* Antipsychotics

Quinagolide

Memantine: effects of dopaminergics possibly enhanced by **memantine**

Methyldopa: antiparkinsonian effect of dopaminergics antagonised by **methyldopa**

Quinapril see ACE Inhibitors

Quinine

- Anti-arrhythmics: increased risk of ventricular arrhythmias when quinine given with **amiodarone**—avoid concomitant use; quinine increases plasma concentration of **flecainide**
- Antibacterials: increased risk of ventricular arrhythmias when quinine given with **moxifloxacin**—avoid concomitant use; plasma concentration of quinine reduced by **rifampicin**
- Anticoagulants: plasma concentration of both drugs increased when quinine given with **warfarin**
- Antidepressants: avoidance of antimalarials advised by manufacturer of **citalopram** and **escitalopram** (risk of ventricular arrhythmias)
- Antimalarials: avoidance of antimalarials advised by manufacturer of **artemether with lumefantrine**; increased risk of ventricular arrhythmias when quinine given with **artemether with lumefantrine**; increased risk of convulsions when quinine given with **mefloquine** (but should not prevent the use of intravenous quinine in severe cases)
- Antipsychotics: increased risk of ventricular arrhythmias when quinine given with **droperidol** or **pimozide**—avoid concomitant use; possible increased risk of ventricular arrhythmias when quinine given with **haloperidol**—avoid concomitant use
- Antivirals: plasma concentration of quinine possibly increased by **atazanavir**, **darunavir**, **fosamprenavir**, **indinavir** and **tipranavir** (increased risk of toxicity); plasma concentration of quinine increased by **ritonavir** (increased risk of toxicity); increased risk of ventricular arrhythmias when quinine given with **squinavir**—avoid concomitant use
- Cardiac Glycosides: quinine increases plasma concentration of **digoxin**
- Dopaminergics: quinine possibly increases plasma concentration of **amantadine**
- Histamine: avoidance of antimalarials advised by manufacturer of **histamine**
- Muscle Relaxants: quinine possibly enhances effects of **suxamethonium**
- Ulcer-healing Drugs: metabolism of quinine inhibited by **cimetidine** (increased plasma concentration)
- Vaccines: antimalarials inactivate **oral typhoid vaccine**—see p. 626

Quinolones

- Analgesics: possible increased risk of convulsions when quinolones given with **NSAIDs**
- Antacids: absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin reduced by **antacids**
- Anti-arrhythmics: increased risk of ventricular arrhythmias when levofloxacin or moxifloxacin given with **amiodarone**—avoid concomitant use; increased risk of ventricular arrhythmias when moxifloxacin given with **disopyramide**—avoid concomitant use
- Antibacterials: increased risk of ventricular arrhythmias when moxifloxacin given with **parenteral erythromycin**—avoid concomitant use; effects of nalidixic acid possibly antagonised by **nitrofurantoin**; possible increased risk of ventricular arrhythmias when moxifloxacin given with **telithromycin**
- Anticoagulants: ciprofloxacin and levofloxacin possibly enhance anticoagulant effect of **coumarins**; nalidixic acid, norfloxacin and ofloxacin enhance anticoagulant effect of **coumarins**; levofloxacin possibly enhances anticoagulant effect of **phenindione**

Quinolones (continued)

- Antidepressants: avoidance of moxifloxacin advised by manufacturer of **citalopram** and **escitalopram** (risk of ventricular arrhythmias); ciprofloxacin inhibits metabolism of **duloxetine**—avoid concomitant use; avoidance of ciprofloxacin advised by manufacturer of **agomelatine**; increased risk of ventricular arrhythmias when moxifloxacin given with **tricyclics**—avoid concomitant use
- Antidiabetics: norfloxacin possibly enhances effects of **glibenclamide**
- Antiepileptics: ciprofloxacin increases or decreases plasma concentration of **phenytoin**
- Antihistamines: increased risk of ventricular arrhythmias when moxifloxacin given with **mizolastine**—avoid concomitant use
- Antimalarials: avoidance of moxifloxacin advised by manufacturer of **piperazine with arteminol** (possible risk of ventricular arrhythmias); avoidance of quinolones advised by manufacturer of **artemether with lumefantrine**; increased risk of ventricular arrhythmias when moxifloxacin given with **chloroquine** and **hydroxychloroquine**, **mefloquine** or **quinine**—avoid concomitant use
- Antipsychotics: increased risk of ventricular arrhythmias when moxifloxacin given with **benperidol**—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when moxifloxacin given with **droperidol**, **haloperidol**, **phenothiazines**, **pimozide** or **zuclopenthixol**—avoid concomitant use; ciprofloxacin increases plasma concentration of **clozapine**; ciprofloxacin possibly increases plasma concentration of **olanzapine**
- Antivirals: manufacturer of norfloxacin advises give **didanosine** at least 2 hours before or after norfloxacin; increased risk of ventricular arrhythmias when moxifloxacin given with **squinavir**—avoid concomitant use
- Atomoxetine: increased risk of ventricular arrhythmias when moxifloxacin given with **atomoxetine**
- Beta-blockers: increased risk of ventricular arrhythmias when moxifloxacin given with **sotalol**—avoid concomitant use
- Calcium Salts: absorption of ciprofloxacin reduced by **calcium salts**
- Ciclosporin: increased risk of nephrotoxicity when quinolones given with **ciclosporin**
- Clopidogrel: ciprofloxacin possibly reduces antiplatelet effect of **clopidogrel**
- Cytotoxics: nalidixic acid increases risk of **melfalan** toxicity; ciprofloxacin possibly reduces excretion of **methotrexate** (increased risk of toxicity); possible increased risk of ventricular arrhythmias when moxifloxacin given with **bosutinib**; ciprofloxacin possibly increases the plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; ciprofloxacin increases plasma concentration of **erlotinib**; possible increased risk of ventricular arrhythmias when moxifloxacin given with **vandetanib**—avoid concomitant use; increased risk of ventricular arrhythmias when levofloxacin or moxifloxacin given with **arsenic trioxide**
- Dairy Products: absorption of ciprofloxacin and norfloxacin reduced by **dairy products**
- Dopaminergics: ciprofloxacin increases plasma concentration of **rasagiline**; ciprofloxacin inhibits metabolism of **ropinirole** (increased plasma concentration)
- 5HT₁-receptor Agonists: quinolones possibly inhibit metabolism of **zolmitriptan** (reduce dose of zolmitriptan)
- Iron: absorption of ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin reduced by **oral iron**; absorp-

QuinolonesIron (*continued*)

tion of norfloxacin reduced by **oral iron** (give at least 2 hours apart)

Lanthanum: absorption of quinolones possibly reduced by **lanthanum** (give at least 2 hours before or 4 hours after lanthanum)

- Muscle Relaxants: ciprofloxacin increases plasma concentration of **tizanidine** (increased risk of toxicity)—avoid concomitant use; norfloxacin possibly increases plasma concentration of **tizanidine** (increased risk of toxicity)

Mycophenolate: norfloxacin possibly reduces bioavailability of **mycophenolate**

- Pentamidine Isetionate: increased risk of ventricular arrhythmias when moxifloxacin given with **pentamidine isetionate**—avoid concomitant use
- Pirfenidone: ciprofloxacin increases plasma concentration of **pirfenidone**—see Cautions under Pirfenidone, BNF section 3.11

Probenecid: excretion of ciprofloxacin, nalidixic acid and norfloxacin reduced by **probenecid** (increased plasma concentration)

Sevelamer: bioavailability of ciprofloxacin reduced by **sevelamer**

Strontium Ranelate: absorption of quinolones reduced by **strontium ranelate** (manufacturer of strontium ranelate advises avoid concomitant use)

- Theophylline: possible increased risk of convulsions when quinolones given with **theophylline**; ciprofloxacin and norfloxacin increase plasma concentration of **theophylline**

Ulcer-healing Drugs: absorption of ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin reduced by **sucralfate**; absorption of norfloxacin reduced by **sucralfate** (give at least 2 hours apart)

Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Zinc: absorption of ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin reduced by **zinc**; absorption of norfloxacin reduced by **zinc** (give at least 2 hours apart)

Rabeprozole *see* Proton Pump Inhibitors

Rabies Vaccine *see* Vaccines

Raloxifene

Anticoagulants: raloxifene antagonises anticoagulant effect of **coumarins**

Lipid-regulating Drugs: absorption of raloxifene reduced by **colestyramine** (manufacturer of raloxifene advises avoid concomitant administration)

Raltegravir

Antacids: absorption of raltegravir possibly reduced by **antacids** (give at least 2 hours apart)

- Antibacterials: plasma concentration of raltegravir reduced by **rifampicin**—consider increasing dose of raltegravir
- Antivirals: increased risk of rash when raltegravir given with **darunavir**; avoidance of raltegravir advised by manufacturer of **fosamprenavir**
- Orlistat: absorption of raltegravir possibly reduced by **orlistat**

Ulcer-healing Drugs: plasma concentration of raltegravir increased by **famotidine** and **omeprazole**

Raltitrexed

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Folate: manufacturer of raltitrexed advises avoid concomitant use with **folates**

Ramipril *see* ACE Inhibitors

Ranitidine *see* Histamine H₂-antagonists

Ranolazine

- Anti-arrhythmics: manufacturer of ranolazine advises avoid concomitant use with **disopyramide**
- Antibacterials: plasma concentration of ranolazine possibly increased by **clarithromycin** and **telithro-**

Ranolazine

• Antibacterials (*continued*)

mycin—manufacturer of ranolazine advises avoid concomitant use; plasma concentration of ranolazine reduced by **rifampicin**—manufacturer of ranolazine advises avoid concomitant use

Antidepressants: plasma concentration of ranolazine increased by **paroxetine**

- Antifungals: plasma concentration of ranolazine possibly increased by **itraconazole**, **posaconazole** and **voriconazole**—manufacturer of ranolazine advises avoid concomitant use

- Antivirals: plasma concentration of ranolazine possibly increased by **atazanavir**, **darunavir**, **fosamprenavir**, **indinavir**, **lopinavir**, **ritonavir**, **saquinavir** and **tipranavir**—manufacturer of ranolazine advises avoid concomitant use

- Beta-blockers: manufacturer of ranolazine advises avoid concomitant use with **sotalol**

Calcium-channel Blockers: plasma concentration of ranolazine increased by **diltiazem** and **verapamil** (consider reducing dose of ranolazine)

Cardiac Glycosides: ranolazine increases plasma concentration of **digoxin**

Ciclosporin: plasma concentration of both drugs may increase when ranolazine given with **ciclosporin**

- Grapefruit Juice: plasma concentration of ranolazine possibly increased by **grapefruit juice**—manufacturer of ranolazine advises avoid concomitant use
- Lipid-regulating Drugs: ranolazine increases plasma concentration of **simvastatin** (see Dose under Simvastatin, BNF section 2.12); manufacturer of lomitapide advises dose reduction when ranolazine given with **lomitapide** (see Dose under Lomitapide, BNF section 2.12)

- Tacrolimus: ranolazine increases plasma concentration of **tacrolimus**

Rasagiline

Note Rasagiline is a MAO-B inhibitor

- Analgesics: avoid concomitant use of rasagiline with **dextromethorphan**; risk of CNS toxicity when rasagiline given with **pethidine** (avoid pethidine for 2 weeks after rasagiline)

Antibacterials: plasma concentration of rasagiline increased by **ciprofloxacin**

- Antidepressants: after stopping rasagiline do not start **fluoxetine** for 2 weeks, also rasagiline should not be started until at least 5 weeks after stopping fluoxetine; after stopping rasagiline do not start **fluvoxamine** for 2 weeks; risk of hypertensive crisis when rasagiline given with **MAOIs**, avoid MAOIs for at least 2 weeks after stopping rasagiline; increased risk of CNS toxicity when rasagiline given with **SSRIs** or **tricyclics**

Dopaminergics: plasma concentration of rasagiline possibly reduced by **entacapone**

Memantine: effects of dopaminergics possibly enhanced by **memantine**

Methyldopa: antiparkinsonian effect of dopaminergics antagonised by **methyldopa**

- Sympathomimetics: avoid concomitant use of rasagiline with **sympathomimetics**

Reboxetine

- Antibacterials: manufacturer of reboxetine advises avoid concomitant use with **macrolides**
- Antidepressants: manufacturer of reboxetine advises avoid concomitant use with **fluvoxamine**; increased risk of hypertension and CNS excitation when reboxetine given with **MAOIs** (MAOIs should not be started until 1 week after stopping reboxetine, avoid reboxetine for 2 weeks after stopping MAOIs)

Antiepileptics: plasma concentration of reboxetine possibly reduced by **carbamazepine** and **phenobarbital**

Reboxetine (continued)

- Antifungals: manufacturer of reboxetine advises avoid concomitant use with **imidazoles** and **triazoles**
- Antimalarials: avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperquine with arteminol**
- Atomoxetine: possible increased risk of convulsions when antidepressants given with **atomoxetine**
- Diuretics: possible increased risk of hypokalaemia when reboxetine given with **loop diuretics** or **thiazides and related diuretics**
- Ergot Alkaloids: possible risk of hypertension when reboxetine given with **ergotamine**

Regorafenib

- Analgesics: manufacturer of regorafenib advises avoid concomitant use with **mefenamic acid**
- Antibacterials: plasma concentration of regorafenib reduced by **rifampicin**—manufacturer of regorafenib advises avoid concomitant use
- Anticoagulants: increased risk of bleeding when regorafenib given with **warfarin**
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Cytotoxics: regorafenib increases plasma concentration of **irinotecan**

Remifentanyl see Opioid Analgesics**Repaglinide** see Antidiabetics**Retigabine**

- Alcohol: increased risk of blurred vision when retigabine given with **alcohol**
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIs** and **tricyclics** (convulsive threshold lowered)
- Antiepileptics: plasma concentration of retigabine possibly reduced by **carbamazepine** and **phenytoin**
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by **mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **antipsychotics** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with **orlistat**

Retinoids

- Alcohol: etretinate formed from acitretin in presence of **alcohol** (increased risk of teratogenicity in women of child-bearing potential)
- Antibacterials: possible increased risk of benign intra-cranial hypertension when retinoids given with **tetracyclines** (avoid concomitant use)
- Anticoagulants: acitretin possibly reduces anticoagulant effect of **coumarins**
- Antiepileptics: isotretinoin possibly reduces plasma concentration of **carbamazepine**
- Antifungals: possible increased risk of tretinoin toxicity when given with **fluconazole** and **voriconazole**
- Cytotoxics: acitretin increases plasma concentration of **methotrexate** (also increased risk of hepatotoxicity)—avoid concomitant use
- Lipid-regulating Drugs: alitretinoin reduces plasma concentration of **simvastatin**
- Vitamins: risk of hypervitaminosis A when retinoids given with **vitamin A**—avoid concomitant use

Ribavirin

- Antivirals: effects of ribavirin possibly reduced by **abacavir**; increased risk of side-effects when ribavirin given with **didanosine**—avoid concomitant use; increased risk of toxicity when ribavirin given with **stavudine**; increased risk of anaemia when ribavirin given with **zidovudine**—avoid concomitant use
- Azathioprine: ribavirin possibly enhances myelosuppressive effects of **azathioprine**

Rifabutin see Rifamycins**Rifampicin** see Rifamycins**Rifamycins**

- Note** Interactions do not apply to rifaximin
- ACE Inhibitors: rifampicin reduces plasma concentration of active metabolite of **imidapril** (reduced anti-hypertensive effect)
- Aliskiren: rifampicin reduces plasma concentration of **aliskiren**
- Ambrisentan: rifampicin possibly increases plasma concentration of **ambrisentan**
- Analgesics: rifampicin reduces plasma concentration of **celecoxib**, **diclofenac** and **etoricoxib**; rifampicin accelerates metabolism of **alfentanil**, **codeine**, **fentanyl**, **methadone** and **morphine** (reduced effect); rifampicin possibly accelerates metabolism of **oxycodone**
- Angiotensin-II Receptor Antagonists: rifampicin reduces plasma concentration of **losartan** and its active metabolite
- Antacids: absorption of rifampicin reduced by **antacids**
- Anti-arrhythmics: rifamycins accelerate metabolism of **disopyramide** (reduced plasma concentration); rifampicin reduces plasma concentration of **dronedarone**—avoid concomitant use; rifampicin accelerates metabolism of **propafenone** (reduced effect)
- Antibacterials: increased risk of side-effects including neutropenia when rifabutin given with **azithromycin**; rifamycins reduce plasma concentration of **clarithromycin** and **dapsone**; plasma concentration of rifabutin increased by **clarithromycin** (increased risk of toxicity—reduce rifabutin dose); plasma concentration of rifabutin possibly increased by **erythromycin** (increased risk of toxicity—reduce rifabutin dose); rifampicin possibly reduces plasma concentration of **tinidazole** and **trimethoprim**; rifampicin reduces plasma concentration of **doxycycline**—consider increasing dose of doxycycline; rifampicin accelerates metabolism of **chloramphenicol** (reduced plasma concentration); increased risk of hepatotoxicity when rifampicin given with **isoniazid**; rifampicin reduces plasma concentration of **linezolid** (possible therapeutic failure of linezolid); rifampicin reduces plasma concentration of **telithromycin** (avoid during and for 2 weeks after rifampicin)
- Anticoagulants: rifampicin reduces plasma concentration of **apixaban**; rifamycins accelerate metabolism of **coumarins** (reduced anticoagulant effect); rifampicin reduces plasma concentration of **dabigatran**—manufacturer of dabigatran advises avoid concomitant use; rifampicin reduces plasma concentration of **rivaroxaban**—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antidiabetics: rifamycins accelerate metabolism of **tolbutamide** (reduced effect); rifampicin reduces plasma concentration of **canagliflozin** and **natagli-nide**; rifampicin possibly reduces effects of **linagliptin**; rifampicin possibly antagonises hypoglycaemic effect of **repaglinide**; rifamycins possibly accelerate metabolism of **sulfonylureas** (reduced effect)
- Antiepileptics: rifabutin reduces plasma concentration of **carbamazepine**; rifampicin reduces plasma concentration of **lamotrigine**; plasma concentration of rifampicin possibly reduced by **phenobarbital**; rifamycins accelerate metabolism of **phenytoin** (reduced plasma concentration)
- Antifungals: plasma concentration of rifabutin increased by **fluconazole** (increased risk of uveitis—reduce rifabutin dose); rifampicin accelerates metabolism of **fluconazole** (reduced plasma concentration); rifabutin and rifampicin reduce plasma concentration of **itraconazole**—manufacturer of itraconazole advises avoid concomitant use; plasma concentration of rifabutin increased by **posaconazole**

Rifamycins● Antifungals (*continued*)

zole (also plasma concentration of posaconazole reduced); rifampicin reduces plasma concentration of **posaconazole** and **terbinafine**; plasma concentration of rifabutin increased by **voriconazole**, also rifabutin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for rifabutin toxicity); rifampicin reduces plasma concentration of **voriconazole**—avoid concomitant use; rifampicin initially increases and then reduces plasma concentration of **caspofungin** (consider increasing dose of caspofungin); plasma concentration of rifabutin possibly increased by **triazoles** (increased risk of uveitis—reduce rifabutin dose)

Antihistamines: rifampicin possibly reduces effects of **fenoxenadine**

- Antimalarials: avoidance of rifampicin advised by manufacturer of **piperquine with arteminol**; rifampicin reduces plasma concentration of **mefloquine**—avoid concomitant use; rifampicin reduces plasma concentration of **quinine**

Antimuscarinics: rifampicin reduces plasma concentration of active metabolite of **fesoterodine**

- Antipsychotics: rifampicin accelerates metabolism of **haloperidol** (reduced plasma concentration); rifabutin and rifampicin possibly reduce plasma concentration of **aripiprazole** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); rifampicin possibly reduces plasma concentration of **clozapine**

- Antivirals: rifampicin possibly reduces plasma concentration of **abacavir**; rifampicin reduces plasma concentration of **atazanavir**, **lopinavir**, **nevirapine** and **rilpivirine**—avoid concomitant use; plasma concentration of rifabutin increased by **atazanavir**, **darunavir**, **fosamprenavir** and **tipranavir** (reduce dose of rifabutin); avoidance of rifampicin advised by manufacturer of **boceprevir** (plasma concentration of boceprevir possibly reduced); rifampicin significantly reduces plasma concentration of

darunavir, **fosamprenavir** and **telaprevir**—avoid concomitant use; rifampicin reduces the plasma concentration of **dolutegravir** (See Dose under Dolutegravir, p. 324); rifampicin reduces plasma concentration of **efavirenz**—increase dose of efavirenz; plasma concentration of rifabutin reduced by **efavirenz**—increase dose of rifabutin; avoidance of rifampicin advised by manufacturer of **elvitegravir**, **etravirine**, **sofosbuvir** and **zidovudine**; rifabutin reduces plasma concentration of **elvitegravir** also plasma concentration of active metabolite of rifabutin increased—reduce dose of rifabutin; plasma concentration of both drugs reduced when rifabutin given with **etravirine**; plasma concentration of rifabutin increased by **indinavir** and **saquinavir** (also plasma concentration of indinavir and saquinavir reduced)—reduce rifabutin dose; rifampicin accelerates metabolism of **indinavir** (reduced plasma concentration—avoid concomitant use); rifampicin reduces plasma concentration of **maraviroc** and **raltegravir**—consider increasing dose of maraviroc and raltegravir; plasma concentration of rifabutin possibly increased by **nevirapine**; rifabutin decreases plasma concentration of **rilpivirine** (increase dose of rilpivirine—consult rilpivirine product literature); plasma concentration of rifabutin increased by **ritonavir** (increased risk of toxicity—reduce rifabutin dose); rifampicin reduces plasma concentration of **ritonavir**; rifampicin significantly reduces plasma concentration of **saquinavir**, also risk of hepatotoxicity—avoid concomitant use; avoidance of rifabutin advised by manufacturer of **sofosbuvir** and **telaprevir**; rifampicin possibly reduces plasma concentration of **tipranavir**—avoid concomitant use

Rifamycins (*continued*)

Anxiolytics and Hypnotics: rifampicin accelerates metabolism of **diazepam** and **zaleplon** (reduced plasma concentration); rifampicin possibly accelerates metabolism of **benzodiazepines** (reduced plasma concentration); rifampicin possibly accelerates metabolism of **buspirone**; rifampicin accelerates metabolism of **zolpidem** (reduced plasma concentration and reduced effect); rifampicin significantly reduces plasma concentration of **zopiclone**

Aprepitant: rifampicin reduces plasma concentration of **aprepitant**

- Atovaquone: avoidance of concomitant rifabutin advised by manufacturer of **atovaquone** (plasma concentration of both drugs reduced); rifampicin reduces plasma concentration of **atovaquone** (and concentration of rifampicin increased)—avoid concomitant use

Beta-blockers: rifampicin accelerates metabolism of **bisoprolol** and **propranolol** (plasma concentration significantly reduced); rifampicin reduces plasma concentration of **carvedilol**, **celiprolol** and **metoprolol**

- Bosentan: rifampicin reduces plasma concentration of **bosentan**—avoid concomitant use

- Calcium-channel Blockers: rifampicin possibly reduces plasma concentration of **felodipine**; rifampicin possibly accelerates metabolism of **nifedipine** (possibly significantly reduced plasma concentration); rifampicin accelerates metabolism of **diltiazem**, **nifedipine**, **nimodipine** and **verapamil** (plasma concentration significantly reduced)

Cardiac Glycosides: rifampicin possibly reduces plasma concentration of **digoxin**

- Ciclosporin: rifampicin accelerates metabolism of **ciclosporin** (reduced plasma concentration)
- Cobicistat: rifabutin reduces plasma concentration of **cobicistat** (adjust dose—consult product literature); rifampicin possibly reduces plasma concentration of **cobicistat**—manufacturer of cobicistat advises avoid concomitant use

- Corticosteroids: rifamycins accelerate metabolism of **corticosteroids** (reduced effect)

- Cytotoxics: rifampicin reduces plasma concentration of **afatinib**, **roxolitinib** and **sorafenib**; rifabutin possibly decreases plasma concentration of **axitinib** (increase dose of axitinib—consult axitinib product literature); rifampicin decreases plasma concentration of **axitinib** (increase dose of axitinib—consult axitinib product literature); rifabutin possibly reduces plasma concentration of **bosutinib** and **crizotinib**—manufacturer of bosutinib and crizotinib advises avoid concomitant use; rifampicin reduces plasma concentration of **bosutinib**, **cabazitaxel**, **crizotinib**, **regorafenib** and **vandetanib**—manufacturer of bosutinib, cabazitaxel, crizotinib, regorafenib and vandetanib advises avoid concomitant use; avoidance of rifampicin advised by manufacturer of **dabrafenib**, **lapatinib** and **vemurafenib**; rifampicin accelerates metabolism of **dasatinib** (reduced plasma concentration—avoid concomitant use); rifampicin accelerates metabolism of **erlotinib** and **sunitinib** (reduced plasma concentration); rifampicin reduces plasma concentration of **everolimus** (avoid concomitant use or consider increasing the dose of everolimus—consult everolimus product literature); rifampicin reduces plasma concentration of **gefitinib**, **imatinib** and **nilotinib**—avoid concomitant use; avoidance of rifabutin advised by manufacturer of **cabazitaxel**, **lapatinib** and **vemurafenib**; rifampicin possibly reduces plasma concentration of **eribulin** and **pazopanib**; rifampicin reduces plasma concentration of active metabolite of **temsirolimus**—avoid concomitant use; rifampicin possibly reduces effects of **brentuximab**

Rifamycins

- Cytotoxics (*continued*)
 - **vedotin**; rifampicin possibly reduces plasma concentration of **vinflunine**—manufacturer of vinflunine advises avoid concomitant use; avoidance of rifampicin advised by manufacturer of **vismodegib** (plasma concentration of vismodegib possibly reduced)

Deferasirox: rifampicin reduces plasma concentration of **deferiasirox**

- Diuretics: rifampicin reduces plasma concentration of **epilorenone**—avoid concomitant use
- Hormone Antagonists: rifabutin possibly reduces plasma concentration of **abiraterone**—manufacturer of abiraterone advises avoid concomitant use; rifampicin reduces plasma concentration of **abiraterone**—manufacturer of abiraterone advises avoid concomitant use; avoidance of rifampicin advised by manufacturer of **enzalutamide**; rifampicin possibly reduces plasma concentration of **exemestane**; rifampicin accelerates metabolism of **tamoxifen** (reduced plasma concentration)

5HT₂-receptor Antagonists: rifampicin accelerates metabolism of **ondansetron** (reduced effect)

- Ivacaftor: rifabutin possibly reduces plasma concentration of **ivacaftor**—manufacturer of ivacaftor advises avoid concomitant use; rifampicin reduces plasma concentration of **ivacaftor**—manufacturer of ivacaftor advises avoid concomitant use

Leflunomide: rifampicin possibly increases plasma concentration of active metabolite of **leflunomide**

Lipid-regulating Drugs: rifampicin possibly reduces plasma concentration of **atorvastatin** and **simvastatin**; rifampicin accelerates metabolism of **fluvastatin** (reduced effect)

- Macitentan: rifampicin reduces plasma concentration of **macitentan**—avoid concomitant use
- Muscle Relaxants: rifampicin possibly reduces plasma concentration of **tizanidine**

- Mycophenolate: rifampicin reduces plasma concentration of active metabolite of **mycophenolate**

- Oestrogens: rifamycins accelerate metabolism of **oestrogens** (reduced contraceptive effect—see p. 402)

- Progestogens: rifamycins accelerate metabolism of **progestogens** (reduced contraceptive effect—see p. 402)

- Ranolazine: rifampicin reduces plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use

- Roflumilast: rifampicin inhibits effects of **roflumilast** (manufacturer of roflumilast advises avoid concomitant use)

- Sirolimus: rifabutin and rifampicin reduce plasma concentration of **sirolimus**—avoid concomitant use

- Tacrolimus: rifabutin possibly reduces plasma concentration of **tacrolimus**; rifampicin reduces plasma concentration of **tacrolimus**

- Tadalafil: rifampicin reduces plasma concentration of **tadalafil**—manufacturer of tadalafil advises avoid concomitant use

Teriflunomide: rifampicin reduces plasma concentration of **teriflunomide**

Theophylline: rifampicin accelerates metabolism of **theophylline** (reduced plasma concentration)

Thyroid Hormones: rifampicin accelerates metabolism of **levothyroxine** (may increase requirements for levothyroxine in hypothyroidism)

Tibolone: rifampicin accelerates metabolism of **tibolone** (reduced plasma concentration)

- Ticagrelor: rifampicin reduces plasma concentration of **ticagrelor**

Tolvaptan: rifampicin reduces plasma concentration of **tolvaptan**

Ulcer-healing Drugs: rifampicin accelerates metabolism of **cimetidine** (reduced plasma concentration)

Rifamycins (*continued*)

- Ulipristal: avoidance of rifampicin advised by manufacturer of **ulipristal** (contraceptive effect of ulipristal possibly reduced)

Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Rilpivirine

Analgesics: rilpivirine possibly reduces plasma concentration of **methadone**

Antacids: manufacturer of rilpivirine advises give **antacids** 2 hours before or 4 hours after rilpivirine

- Antibacterials: manufacturer of rilpivirine advises avoid concomitant use with **clarithromycin** and **erythromycin** (plasma concentration of rilpivirine possibly increased); plasma concentration of rilpivirine decreased by **rifabutin** (increase dose of rilpivirine—consult rilpivirine product literature); plasma concentration of rilpivirine reduced by **rifampicin**—avoid concomitant use

Anticoagulants: rilpivirine possibly increases plasma concentration of **dabigatran**

- Antidepressants: manufacturer of rilpivirine advises avoid concomitant use with **St John's wort** (plasma concentration of rilpivirine possibly reduced)

- Antiepileptics: manufacturer of rilpivirine advises avoid concomitant use with **carbamazepine**, **oxcarbazepine**, **phenobarbital** and **phenytoin** (plasma concentration of rilpivirine possibly reduced)

Antivirals: manufacturer of rilpivirine advises give **didanosine** 2 hours before or 4 hours after rilpivirine; avoidance of rilpivirine advised by manufacturer of **nevirapine**

Calcium Salts: manufacturer of rilpivirine advises give **calcium salts** 2 hours before or 4 hours after rilpivirine

- Corticosteroids: manufacturer of rilpivirine advises avoid concomitant use with **dexamethasone** (except when given as a single dose)

- Orlistat: absorption of rilpivirine possibly reduced by **orlistat**

- Ulcer-healing Drugs: manufacturer of rilpivirine advises avoid concomitant use with **esomeprazole**, **lansoprazole**, **pantoprazole** and **rabeprazole** (plasma concentration of rilpivirine possibly reduced); plasma concentration of rilpivirine reduced by **omeprazole**—avoid concomitant use; manufacturer of rilpivirine advises avoid **histamine H₂-antagonists** for 12 hours before or 4 hours after rilpivirine—consult product literature

Risedronate Sodium *see* Bisphosphonates

Risperidone *see* Antipsychotics

Ritonavir

- Alpha-blockers: ritonavir possibly increases plasma concentration of **alfuzosin**—avoid concomitant use
- Analgesics: ritonavir possibly increases plasma concentration of **NSAIDs** and **buprenorphine**; ritonavir increases plasma concentration of **dextropropoxyphene** and **piroxicam** (risk of toxicity)—avoid concomitant use; ritonavir increases plasma concentration of **alfentanil** and **fentanyl**; ritonavir reduces plasma concentration of **methadone**; ritonavir possibly reduces plasma concentration of **morphine**; ritonavir reduces plasma concentration of **pethidine**, but increases plasma concentration of toxic metabolite of pethidine (avoid concomitant use)
- Anti-arrhythmics: ritonavir increases plasma concentration of **amiodarone** and **propafenone** (increased risk of ventricular arrhythmias—avoid concomitant use); ritonavir possibly increases plasma concentration of **disopyramide** (increased risk of toxicity); avoidance of ritonavir advised by manufacturer of **dronedarone**; ritonavir possibly increases plasma concentration of

Ritonavir

- Anti-arrhythmics (*continued*)
 - **flecainide** (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antibacterials: ritonavir possibly increases plasma concentration of **azithromycin** and **erythromycin**; ritonavir increases plasma concentration of **clarithromycin** (reduce dose of clarithromycin in renal impairment); ritonavir increases plasma concentration of **rifabutin** (increased risk of toxicity—reduce rifabutin dose); plasma concentration of ritonavir reduced by **rifampicin**; plasma concentration of both drugs increased when ritonavir given with **fusidic acid**—avoid concomitant use; avoidance of concomitant ritonavir in severe renal and hepatic impairment advised by manufacturer of **telithromycin**
- Anticoagulants: ritonavir may enhance or reduce anticoagulant effect of **warfarin**; avoidance of ritonavir advised by manufacturer of **apixaban**; ritonavir possibly enhances anticoagulant effect of **coumarins** and **phenindione**; ritonavir increases plasma concentration of **rivaroxaban**—avoid concomitant use
- Antidepressants: ritonavir possibly reduces plasma concentration of **paroxetine**; ritonavir increases plasma concentration of **trazodone** (increased risk of toxicity); ritonavir possibly increases plasma concentration of **SSRIs** and **tricyclics**; plasma concentration of ritonavir reduced by **St John's wort**—avoid concomitant use
- Antidiabetics: ritonavir possibly increases plasma concentration of **tolbutamide**
- Antiepileptics: ritonavir possibly increases plasma concentration of **carbamazepine**; ritonavir possibly reduces plasma concentration of **lamotrigine** and **valproate**; plasma concentration of ritonavir possibly reduced by **phenytoin**, also plasma concentration of phenytoin possibly affected
- Antifungals: plasma concentration of ritonavir increased by **fluconazole**; combination of ritonavir with **itraconazole** may increase plasma concentration of either drug (or both); ritonavir reduces plasma concentration of **voriconazole**—avoid concomitant use
- Antihistamines: ritonavir possibly increases plasma concentration of **non-sedating antihistamines**
- Antimalarials: caution with ritonavir advised by manufacturer of **artemether with lumefantrine**; plasma concentration of ritonavir possibly reduced by **mefloquine**; ritonavir increases plasma concentration of **quinine** (increased risk of toxicity)
- Antimuscarinics: avoidance of ritonavir advised by manufacturer of **darifenacin** and **tolterodine**; manufacturer of fesoterodine advises dose reduction when ritonavir given with **fesoterodine**—consult fesoterodine product literature; ritonavir possibly increases plasma concentration of **solifenacin**—see Dose under Solifenacin, BNF section 7.4.2
- Antipsychotics: ritonavir possibly increases plasma concentration of **antipsychotics**; ritonavir possibly increases plasma concentration of **aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); manufacturer of ritonavir advises avoid concomitant use with **clozapine** (increased risk of toxicity); ritonavir reduces plasma concentration of **olanzapine**—consider increasing dose of olanzapine; ritonavir increases plasma concentration of **pimozide** (increased risk of ventricular arrhythmias—avoid concomitant use); ritonavir possibly increases plasma concentration of **quetiapine**—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: plasma concentration of both drugs reduced when ritonavir given with **boceprevir**; manufacturer of ritonavir advises ritonavir and **didanosine** should be taken 2.5 hours apart; ritonavir

Ritonavir

- Antivirals (*continued*)
 - increases the toxicity of **efavirenz**, monitor liver function tests —manufacturer of **Atripla**® advises avoid concomitant use with **high-dose** ritonavir; ritonavir increases plasma concentration of **indinavir**, **maraviroc** and **sacquinavir**; ritonavir possibly reduces plasma concentration of **telaprevir**
- Anxiolytics and Hypnotics: ritonavir possibly increases plasma concentration of **anxiolytics** and **hypnotics**; ritonavir possibly increases plasma concentration of **alprazolam**, **diazepam**, **flurazepam** and **zolpidem** (risk of extreme sedation and respiratory depression—avoid concomitant use); ritonavir possibly increases plasma concentration of **midazolam** (risk of prolonged sedation—avoid concomitant use of oral midazolam); ritonavir increases plasma concentration of **buspirone** (increased risk of toxicity)
- Aprepitant: ritonavir possibly increases plasma concentration of **aprepitant**
- Atovaquone: ritonavir possibly reduces plasma concentration of **atovaquone**—manufacturer of atovaquone advises avoid concomitant use
- Bosentan: ritonavir increases plasma concentration of **bosentan** (consider reducing dose of bosentan)
- Bupropion: ritonavir reduces plasma concentration of **bupropion**
- Calcium-channel Blockers: ritonavir possibly increases plasma concentration of **calcium-channel blockers**; avoidance of ritonavir advised by manufacturer of **lercanidipine**
- Cardiac Glycosides: ritonavir possibly increases plasma concentration of **digoxin**
- Ciclosporin: ritonavir possibly increases plasma concentration of **ciclosporin**
- Cilostazol: ritonavir possibly increases plasma concentration of **cilostazol** (see Dose under Cilostazol, BNF section 2.6.4)
- Colchicine: ritonavir possibly increases risk of **colchicine** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: ritonavir possibly increases plasma concentration of **corticosteroids**—increased risk of adrenal suppression; ritonavir possibly increases plasma concentration of **budesonide** (including **inhaled**, **intranasal**, and **rectal** budesonide)—increased risk of adrenal suppression; ritonavir increases plasma concentration of **inhaled** and **intranasal** **fluticasone**—increased risk of adrenal suppression
- Cytotoxics: ritonavir increases the plasma concentration of **afatinib**—manufacturer of afatinib advises separating administration of ritonavir by 6 to 12 hours; ritonavir possibly increases plasma concentration of **axitinib** (reduce dose of axitinib—consult axitinib product literature); ritonavir possibly increases the plasma concentration of **bosutinib** and **cabazitaxel**—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; ritonavir possibly increases plasma concentration of **crizotinib**, **everolimus**, **nilotinib** and **vinflunine**—manufacturer of crizotinib, everolimus, nilotinib and vinflunine advises avoid concomitant use; avoidance of ritonavir advised by manufacturer of **lapatinib**; ritonavir possibly increases plasma concentration of **pazopanib** (reduce dose of pazopanib); manufacturer of ruxolitinib advises dose reduction when ritonavir given with **ruxolitinib**—consult ruxolitinib product literature; ritonavir possibly increases plasma concentration of **docetaxel** (increased risk of toxicity); ritonavir increases plasma concentration of **paclitaxel**; ritonavir possibly increases plasma concentration of **vinblastine**

Ritonavir (*continued*)

- Dapoxetine: avoidance of ritonavir advised by manufacturer of **dapoxetine** (increased risk of toxicity)
- Diuretics: ritonavir increases plasma concentration of **eplerenone**—avoid concomitant use
- Ergot Alkaloids: increased risk of ergotism when ritonavir given with **ergotamine**—avoid concomitant use
- 5HT₁-receptor Agonists: ritonavir increases plasma concentration of **eletriptan** (risk of toxicity)—avoid concomitant use
- Ivabradine: ritonavir possibly increases plasma concentration of **ivabradine**—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when ritonavir given with **atorvastatin**; possible increased risk of myopathy when ritonavir given with **rosuvastatin**—manufacturer of rosuvastatin advises avoid concomitant use; increased risk of myopathy when ritonavir given with **simvastatin** (avoid concomitant use); avoidance of ritonavir advised by manufacturer of **lomitapide** (plasma concentration of lomitapide possibly increased)
- Mirabegron: when given with ritonavir avoid or reduce dose of **mirabegron** in hepatic or renal impairment—see Mirabegron, BNF section 7.4.2
- Oestrogens: ritonavir accelerates metabolism of **oestrogens** (reduced contraceptive effect—see p. 402)
- Orlistat: absorption of ritonavir possibly reduced by **orlistat**
- Ranolazine: ritonavir possibly increases plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: ritonavir significantly increases plasma concentration of **sildenafil**—avoid concomitant use
- Sympathomimetics: ritonavir possibly increases plasma concentration of **dexamfetamine**
- Sympathomimetics, Beta₂: manufacturer of ritonavir advises avoid concomitant use with **salmeterol**
- Tacrolimus: ritonavir possibly increases plasma concentration of **tacrolimus**
- Tadalafil: ritonavir increases plasma concentration of **tadalafil**—manufacturer of tadalafil advises avoid concomitant use
- Theophylline: ritonavir accelerates metabolism of **theophylline** (reduced plasma concentration)
- Ticagrelor: ritonavir possibly increases plasma concentration of **ticagrelor**—manufacturer of ticagrelor advises avoid concomitant use
- Ulipristal: avoidance of ritonavir advised by manufacturer of **ulipristal** (contraceptive effect of ulipristal possibly reduced)
- Vardenafil: ritonavir increases plasma concentration of **vardenafil**—avoid concomitant use

Rivaroxaban

- Analgesics: increased risk of haemorrhage when anticoagulants given with **intravenous diclofenac** (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with **ketorolac** (avoid concomitant use, including low-dose heparins)
- Anti-arrhythmics: manufacturer of rivaroxaban advises avoid concomitant use with **dronedarone**
- Antibacterials: plasma concentration of rivaroxaban reduced by **rifampicin**—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Anticoagulants: increased risk of haemorrhage when rivaroxaban given with other **anticoagulants** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when other anticoagulants given with **apixaban** and **dabigatran** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Rivaroxaban (*continued*)

- Antidepressants: plasma concentration of rivaroxaban possibly reduced by **St John's wort**—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antiepileptics: plasma concentration of rivaroxaban possibly reduced by **carbamazepine**, **phenobarbital** and **phenytoin**—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antifungals: manufacturer of rivaroxaban advises avoid concomitant use with **itraconazole**, **posaconazole** and **voriconazole**
- Antivirals: manufacturer of rivaroxaban advises avoid concomitant use with **atazanavir**, **darunavir**, **fosamprenavir**, **indinavir**, **saquinavir** and **tipranavir**; manufacturers advise avoid concomitant use of rivaroxaban with **lopinavir**; plasma concentration of rivaroxaban increased by **ritonavir**—avoid concomitant use
- Cobicistat: anticoagulant effect of rivaroxaban possibly enhanced by **cobicistat**—avoid concomitant use

Rivastigmine *see* Parasympathomimetics

Rizatriptan *see* 5HT₁-receptor Agonists (under HT)

Rocuronium *see* Muscle Relaxants

Roflumilast

- Antibacterials: effects of roflumilast inhibited by **rifampicin** (manufacturer of roflumilast advises avoid concomitant use)
- Antidepressants: metabolism of roflumilast inhibited by **fluvoxamine**
- Antiepileptics: effects of roflumilast possibly inhibited by **carbamazepine**, **phenobarbital** and **phenytoin** (manufacturer of roflumilast advises avoid concomitant use)
- Theophylline: manufacturer of roflumilast advises avoid concomitant use with **theophylline**
- Ulcer-healing Drugs: metabolism of roflumilast inhibited by **cimetidine**

Ropinirole

- Antibacterials: metabolism of ropinirole inhibited by **ciprofloxacin** (increased plasma concentration)
- Antipsychotics: manufacturer of ropinirole advises avoid concomitant use of **antipsychotics** (antagonism of effect)
- Memantine: effects of dopaminergics possibly enhanced by **memantine**
- Methyl dopa: antiparkinsonian effect of dopaminergics antagonised by **methyl dopa**
- Metoclopramide: manufacturer of ropinirole advises avoid concomitant use of **metoclopramide** (antagonism of effect)
- Oestrogens: plasma concentration of ropinirole increased by **oestrogens**

Ropivacaine

- Anti-arrhythmics: increased myocardial depression when ropivacaine given with **anti-arrhythmics**
- Antidepressants: metabolism of ropivacaine inhibited by **fluvoxamine**—avoid prolonged administration of ropivacaine

Rosuvastatin *see* Statins

Rotigotine

- Antipsychotics: manufacturer of rotigotine advises avoid concomitant use of **antipsychotics** (antagonism of effect)
- Memantine: effects of dopaminergics possibly enhanced by **memantine**
- Methyl dopa: antiparkinsonian effect of dopaminergics antagonised by **methyl dopa**
- Metoclopramide: manufacturer of rotigotine advises avoid concomitant use of **metoclopramide** (antagonism of effect)

Rufinamide

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **tricyclics**

Rufinamide

- Antidepressants (*continued*)
 related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by ●SSRIs and ●tricyclics (convulsive threshold lowered)
 Antiepileptics: plasma concentration of both drugs possibly reduced when rufinamide given with ●carbamazepine; plasma concentration of rufinamide possibly reduced by ●phenobarbital; plasma concentration of rufinamide possibly reduced by ●phenytoin, also plasma concentration of phenytoin possibly increased; plasma concentration of rufinamide possibly increased by ●valproate (reduce dose of rufinamide)
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by ●mefloquine
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ●antipsychotics (convulsive threshold lowered)
- Oestrogens: rufinamide accelerates metabolism of ●oestrogens (reduced contraceptive effect—see p. 402)
- Orlistat: possible increased risk of convulsions when antiepileptics given with ●orlistat
- Progestogens: rufinamide accelerates metabolism of ●progestogens (reduced contraceptive effect—see p. 402)

Rupatadine see Antihistamines

Ruxolitinib

- Antibacterials: manufacturer of ruxolitinib advises dose reduction when ruxolitinib given with ●clarithromycin and ●telithromycin—consult ruxolitinib product literature; plasma concentration of ruxolitinib reduced by ●rifampicin
- Antifungals: manufacturer of ruxolitinib advises dose reduction when ruxolitinib given with ●fluconazole, ●itraconazole, ●posaconazole and ●voriconazole—consult ruxolitinib product literature
- Antipsychotics: avoid concomitant use of cytotoxics with ●clozapine (increased risk of agranulocytosis)
- Antivirals: manufacturer of ruxolitinib advises dose reduction when ruxolitinib given with ●boceprevir, ●indinavir, ●lopinavir, ●ritonavir, ●saquinavir and ●telaprevir—consult ruxolitinib product literature

St John's Wort

- Analgesics: St John's wort possibly reduces plasma concentration of ●methadone
- Anti-arrhythmics: St John's wort possibly reduces plasma concentration of ●dronedronone—avoid concomitant use
 - Antibacterials: St John's wort reduces plasma concentration of ●telithromycin (avoid during and for 2 weeks after St John's wort)
 - Anticoagulants: St John's wort reduces anticoagulant effect of ●coumarins (avoid concomitant use); St John's wort possibly reduces plasma concentration of ●dabigatran—manufacturer of dabigatran advises avoid concomitant use; St John's wort possibly reduces plasma concentration of ●rivaroxaban—manufacturer of rivaroxaban advises monitor for signs of thrombosis
 - Antidepressants: possible increased serotonergic effects when St John's wort given with ●duloxetine or ●venlafaxine; St John's wort reduces plasma concentration of ●amitriptyline; increased serotonergic effects when St John's wort given with ●SSRIs—avoid concomitant use
 - Antiepileptics: St John's wort possibly reduces plasma concentration of ●carbamazepine; St John's wort possibly reduces plasma concentration of ●phenobarbital and ●phenytoin—avoid concomitant use
 - Antifungals: St John's wort reduces plasma concentration of ●voriconazole—avoid concomitant use
- St John's Wort** (*continued*)
- Antimalarials: avoidance of antidepressants advised by manufacturer of ●artemether with lumefantrine and ●piperaquine with arteminol
 - Antipsychotics: St John's wort possibly reduces plasma concentration of ●aripiprazole (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature)
 - Antivirals: St John's wort reduces plasma concentration of ●atazanavir, ●darunavir, ●efavirenz, ●fosamprenavir, ●indinavir, ●lopinavir, ●nevirapine, ●ritonavir and ●saquinavir—avoid concomitant use; avoidance of St John's wort advised by manufacturer of ●dolutegravir, ●elvitegravir, ●etravirine, ●sofosbuvir and ●telaprevir; St John's wort possibly reduces plasma concentration of ●maraviroc and ●tipranavir—avoid concomitant use; avoidance of St John's wort advised by manufacturer of ●rilpivirine (plasma concentration of rilpivirine possibly reduced)
- Anxiolytics and Hypnotics: St John's wort possibly reduces plasma concentration of oral ●midazolam
- Aprepitant: avoidance of St John's wort advised by manufacturer of ●aprepitant
- Atomoxetine: possible increased risk of convulsions when antidepressants given with ●atomoxetine
- Calcium-channel Blockers: St John's wort possibly reduces plasma concentration of ●amlodipine and ●felodipine; St John's wort reduces plasma concentration of ●nifedipine; St John's wort significantly reduces plasma concentration of ●verapamil
 - Cardiac Glycosides: St John's wort reduces plasma concentration of ●digoxin—avoid concomitant use
 - Ciclosporin: St John's wort reduces plasma concentration of ●ciclosporin—avoid concomitant use
 - Cobicistat: St John's wort possibly reduces plasma concentration of ●cobicistat—manufacturer of cobicistat advises avoid concomitant use
 - Cytotoxics: St John's wort possibly reduces plasma concentration of ●axitinib—consider increasing dose of axitinib; St John's wort possibly reduces plasma concentration of ●bosutinib, ●crizotinib, ●everolimus and ●vinflunine—manufacturer of bosutinib, crizotinib, everolimus and vinflunine advises avoid concomitant use; avoidance of St John's wort advised by manufacturer of ●cabazitaxel, ●dabrafenib, ●gefitinib, ●lapatinib and ●vemurafenib; St John's wort reduces plasma concentration of ●imatinib—avoid concomitant use; avoidance of St John's wort advised by manufacturer of ●vandetanib and ●vismodegib (plasma concentration of vandetanib and vismodegib possibly reduced); St John's wort possibly reduces plasma concentration of ●eribulin; St John's wort accelerates metabolism of ●irinotecan (reduced plasma concentration—avoid concomitant use)
 - Dapoxetine: possible increased risk of serotonergic effects when St John's wort given with ●dapoxetine (manufacturer of dapoxetine advises St John's wort should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping St John's wort)
 - Diuretics: St John's wort reduces plasma concentration of ●eplerenone—avoid concomitant use
 - Hormone Antagonists: St John's wort possibly reduces plasma concentration of ●abiraterone—manufacturer of abiraterone advises avoid concomitant use
 - 5HT₁-receptor Agonists: increased serotonergic effects when St John's wort given with ●5HT₁ agonists—avoid concomitant use
- Ivabradine: St John's wort reduces plasma concentration of ●ivabradine—avoid concomitant use
- Ivacaftor: St John's wort possibly reduces plasma concentration of ●ivacaftor—manufacturer of ivacaftor advises avoid concomitant use

St John's Wort (*continued*)

Lipid-regulating Drugs: St John's wort reduces plasma concentration of **simvastatin**

Macitentan: avoidance of St John's wort advised by manufacturer of **macitentan**

- Oestrogens: St John's wort reduces contraceptive effect of **oestrogens** (avoid concomitant use)
- Progestogens: St John's wort reduces contraceptive effect of **progestogens** (avoid concomitant use)
- Tacrolimus: St John's wort reduces plasma concentration of **tacrolimus**—avoid concomitant use
- Theophylline: St John's wort possibly reduces plasma concentration of **theophylline**
- Ulcer-healing Drugs: St John's wort possibly reduces plasma concentration of **omeprazole**
- Ulipristal: avoidance of St John's wort advised by manufacturer of **ulipristal** (contraceptive effect of ulipristal possibly reduced)

Salbutamol *see* Sympathomimetics, Beta₂

Salmeterol *see* Sympathomimetics, Beta₂

Saquinavir

- Analgesics: increased risk of ventricular arrhythmias when saquinavir given with **alfentanil**, **fentanyl** or **methadone**—avoid concomitant use
- Anti-arrhythmics: increased risk of ventricular arrhythmias when saquinavir given with **amiodarone**, **disopyramide**, **dronedaron**, **flecainide**, **lidocaine** or **propafenone**—avoid concomitant use
- Antibacterials: plasma concentration of both drugs possibly increased when saquinavir given with **clarithromycin** (increased risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when saquinavir given with **dapsone**, **erythromycin** or **moxifloxacin**—avoid concomitant use; saquinavir increases plasma concentration of **rifabutin** (also plasma concentration of saquinavir reduced)—reduce rifabutin dose; plasma concentration of saquinavir significantly reduced by **rifampicin**, also risk of hepatotoxicity—avoid concomitant use; plasma concentration of both drugs may increase when saquinavir given with **fusidic acid**; avoidance of saquinavir advised by manufacturer of **telithromycin** (risk of ventricular arrhythmias)
- Anticoagulants: saquinavir possibly enhances anticoagulant effect of **warfarin**; avoidance of saquinavir advised by manufacturer of **apixaban** and **rivaroxaban**
- Antidepressants: increased risk of ventricular arrhythmias when saquinavir given with **trazodone** or **tricyclics**—avoid concomitant use; plasma concentration of saquinavir reduced by **St John's wort**—avoid concomitant use
- Antiepileptics: plasma concentration of saquinavir possibly reduced by **carbamazepine**, **phenobarbital** and **phenytoin**
- Antifungals: plasma concentration of saquinavir possibly increased by **imidazoles** and **triazoles**
- Antihistamines: increased risk of ventricular arrhythmias when saquinavir given with **mizolastine**—avoid concomitant use
- Antimalarials: avoidance of saquinavir advised by manufacturer of **piperaquine with arteminol** (possible risk of ventricular arrhythmias); caution with saquinavir advised by manufacturer of **artemether with lumefantrine**; increased risk of ventricular arrhythmias when saquinavir given with **quinine**—avoid concomitant use
- Antimuscarinics: avoidance of saquinavir advised by manufacturer of **darifenacin** and **tolterodine**; manufacturer of fesoterodine advises dose reduction when saquinavir given with **fesoterodine**—consult fesoterodine product literature
- Antipsychotics: increased risk of ventricular arrhythmias when saquinavir given with **clozapine**, **haloperidol** or **phenothiazines**—avoid concomitant use; saquinavir possibly increases plasma concentration

Saquinavir• Antipsychotics (*continued*)

of **aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); saquinavir possibly increases plasma concentration of **pimozide** (increased risk of ventricular arrhythmias—avoid concomitant use); saquinavir possibly increases plasma concentration of **quetiapine**—manufacturer of quetiapine advises avoid concomitant use

- Antivirals: increased risk of ventricular arrhythmias when saquinavir given with **atazanavir** or **lopinavir**—avoid concomitant use; saquinavir reduces plasma concentration of **darunavir**; plasma concentration of saquinavir significantly reduced by **efavirenz**; plasma concentration of saquinavir increased by **indinavir** and **ritonavir**; saquinavir increases plasma concentration of **maraviroc** (consider reducing dose of maraviroc); plasma concentration of saquinavir reduced by **tipranavir**

- Anxiolytics and Hypnotics: saquinavir increases plasma concentration of **midazolam** (risk of prolonged sedation—avoid concomitant use of oral midazolam)

- Beta-blockers: increased risk of ventricular arrhythmias when saquinavir given with **sotalol**—avoid concomitant use

- Ciclosporin: plasma concentration of both drugs increased when saquinavir given with **ciclosporin**

Corticosteroids: plasma concentration of saquinavir possibly reduced by **dexamethasone**

- Cytotoxics: saquinavir possibly increases the plasma concentration of **afatinib**—manufacturer of afatinib advises separating administration of saquinavir by 6 to 12 hours; saquinavir possibly increases plasma concentration of **axitinib** (reduce dose of axitinib—consult axitinib product literature); saquinavir possibly increases the plasma concentration of **bosutinib** and **cabazitaxel**—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; saquinavir possibly increases plasma concentration of **crizotinib** and **everolimus**—manufacturer of crizotinib and everolimus advises avoid concomitant use; avoidance of saquinavir advised by manufacturer of **lapatinib**; increased risk of ventricular arrhythmias when saquinavir given with **pazopanib**—avoid concomitant use; manufacturer of ruxolitinib advises dose reduction when saquinavir given with **ruxolitinib**—consult ruxolitinib product literature

- Dapoxetine: avoidance of saquinavir advised by manufacturer of **dapoxetine** (increased risk of toxicity)

Diuretics: saquinavir increases plasma concentration of **eplerenone** (reduce dose of eplerenone)

- Ergot Alkaloids: increased risk of ergotism when saquinavir given with **ergotamine**—avoid concomitant use

- Lipid-regulating Drugs: possible increased risk of myopathy when saquinavir given with **atorvastatin**; possible increased risk of myopathy when saquinavir given with **rosuvastatin**—manufacturer of rosuvastatin advises avoid concomitant use; increased risk of myopathy when saquinavir given with **simvastatin** (avoid concomitant use); avoidance of saquinavir advised by manufacturer of **lomitapide** (plasma concentration of lomitapide possibly increased)

- Orlistat: absorption of saquinavir possibly reduced by **orlistat**

- Pentamidine Isetionate: increased risk of ventricular arrhythmias when saquinavir given with **pentamidine isetionate**—avoid concomitant use

- Ranolazine: saquinavir possibly increases plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use

Saquinavir (*continued*)

- Sildenafil: increased risk of ventricular arrhythmias when saquinavir given with ●**sildenafil**—avoid concomitant use
- Tacrolimus: saquinavir increases plasma concentration of ●**tacrolimus** (consider reducing dose of tacrolimus)
- Tadalafil: increased risk of ventricular arrhythmias when saquinavir given with ●**tadalafil**—avoid concomitant use
- Ulcer-healing Drugs: plasma concentration of saquinavir possibly increased by ●**cimetidine**; plasma concentration of saquinavir possibly increased by ●**esomeprazole**, ●**lansoprazole**, ●**pantoprazole** and ●**rabeprazole**—manufacturer of saquinavir advises avoid concomitant use; plasma concentration of saquinavir increased by ●**omeprazole**—manufacturer of saquinavir advises avoid concomitant use
- Vardenafil: increased risk of ventricular arrhythmias when saquinavir given with ●**vardenafil**—avoid concomitant use

Saxagliptin *see* Antidiabetics**Selegiline**

Note Selegiline is a MAO-B inhibitor

- Analgesics: hyperpyrexia and CNS toxicity reported when selegiline given with ●**pethidine** (avoid concomitant use); manufacturer of selegiline advises avoid concomitant use with ●**opioid analgesics**
- Antidepressants: manufacturer of selegiline advises avoid concomitant use with ●**citalopram** and ●**escitalopram**; increased risk of hypertension and CNS excitation when selegiline given with ●**fluoxetine** (selegiline should not be started until 5 weeks after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when selegiline given with ●**fluvoxamine**, ●**sertraline** or ●**venlafaxine** (selegiline should not be started until 1 week after stopping fluvoxamine, sertraline or venlafaxine, avoid fluvoxamine, sertraline or venlafaxine for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when selegiline given with ●**paroxetine** (selegiline should not be started until 2 weeks after stopping paroxetine, avoid paroxetine for 2 weeks after stopping selegiline); enhanced hypotensive effect when selegiline given with ●**MAOIs**—manufacturer of selegiline advises avoid concomitant use; avoid concomitant use of selegiline with ●**moclobemide**; CNS toxicity reported when selegiline given with ●**tricyclics**
- Dopaminergics: max. dose of 10mg selegiline advised by manufacturer of ●**entacapone** if used concomitantly; selegiline enhances effects and increases toxicity of ●**levodopa** (reduce dose of levodopa)
- 5HT₁-receptor Agonists: manufacturer of selegiline advises avoid concomitant use with 5HT₁ agonists
- Memantine: effects of dopaminergics and selegiline possibly enhanced by ●**memantine**
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by ●**methyldopa**
- Oestrogens: plasma concentration of selegiline increased by ●**oestrogens**—manufacturer of selegiline advises avoid concomitant use
- Progestogens: plasma concentration of selegiline increased by ●**progestogens**—manufacturer of selegiline advises avoid concomitant use
- Sympathomimetics: manufacturer of selegiline advises avoid concomitant use with ●**sympathomimetics**; risk of hypertensive crisis when selegiline given with ●**dopamine**

Selenium

- Eltrombopag: selenium possibly reduces absorption of ●**eltrombopag** (give at least 4 hours apart)
- Vitamins: absorption of selenium possibly reduced by ●**ascorbic acid** (give at least 4 hours apart)

Sertraline *see* Antidepressants, SSRI**Sevelamer**

Antibacterials: sevelamer reduces bioavailability of ●**ciprofloxacin**

Ciclosporin: sevelamer possibly reduces plasma concentration of ●**ciclosporin**

Mycophenolate: sevelamer possibly reduces plasma concentration of ●**mycophenolate**

Tacrolimus: sevelamer possibly reduces plasma concentration of ●**tacrolimus**

Thyroid Hormones: sevelamer possibly reduces absorption of ●**levothyroxine**

Vitamins: sevelamer reduces absorption of ●**calcitriol** (give at least 1 hour before or 3 hours after sevelamer)

Sevoflurane *see* Anaesthetics, General**Sildenafil**

- Alpha-blockers: enhanced hypotensive effect when sildenafil given with ●**alpha-blockers** (avoid alpha-blockers for 4 hours after sildenafil)—*see* also under Phosphodiesterase type-5 inhibitors, BNF section 7.4.5
- Anti-arrhythmics: avoidance of sildenafil advised by manufacturer of ●**disopyramide** (risk of ventricular arrhythmias)
- Antibacterials: plasma concentration of sildenafil increased by ●**clarithromycin** (consider reducing dose of sildenafil); plasma concentration of sildenafil increased by ●**erythromycin**—reduce initial dose of sildenafil; plasma concentration of sildenafil possibly increased by ●**telithromycin**—reduce initial dose of sildenafil
- Antifungals: plasma concentration of sildenafil increased by ●**itraconazole**—reduce initial dose of sildenafil
- Antivirals: side-effects of sildenafil possibly increased by ●**atazanavir**; plasma concentration of sildenafil reduced by ●**etravirine**; plasma concentration of sildenafil possibly increased by ●**fosamprenavir**; plasma concentration of sildenafil increased by ●**indinavir**—reduce initial dose of sildenafil; plasma concentration of sildenafil significantly increased by ●**ritonavir**—avoid concomitant use; increased risk of ventricular arrhythmias when sildenafil given with ●**saquinavir**—avoid concomitant use; avoidance of sildenafil advised by manufacturer of ●**telaprevir**
- Bosentan: plasma concentration of sildenafil reduced by ●**bosentan**, also plasma concentration of bosentan increased
- Calcium-channel Blockers: enhanced hypotensive effect when sildenafil given with ●**amlodipine**
- Cobicistat: plasma concentration of sildenafil possibly increased by ●**cobicistat**—manufacturer of cobicistat advises avoid concomitant use of sildenafil for pulmonary arterial hypertension or reduce dose of sildenafil for erectile dysfunction—consult cobicistat product literature
- Dapoxetine: avoidance of sildenafil advised by manufacturer of ●**dapoxetine**
- Grapefruit Juice: plasma concentration of sildenafil possibly increased by ●**grapefruit juice**
- Nicorandil: sildenafil significantly enhances hypotensive effect of ●**nicorandil** (avoid concomitant use)
- Nitrates: sildenafil significantly enhances hypotensive effect of ●**nitrates** (avoid concomitant use)
- Ulcer-healing Drugs: plasma concentration of sildenafil increased by ●**cimetidine** (consider reducing dose of sildenafil)

Simvastatin *see* Statins**Sirolimus**

Anti-arrhythmics: caution with sirolimus advised by manufacturer of ●**dronedarone**

- Antibacterials: plasma concentration of sirolimus increased by ●**clarithromycin** and ●**telithromycin**—avoid concomitant use; plasma concentration of both drugs increased when sirolimus given with ●**erythromycin**; plasma concentration of sirolimus

Sirolimus

- Antibacterials (*continued*)
reduced by ●**rifabutin** and ●**rifampicin**—avoid concomitant use
- Antifungals: plasma concentration of sirolimus increased by ●**miconazole**; plasma concentration of sirolimus possibly increased by ●**fluconazole** and ●**posaconazole**; plasma concentration of sirolimus increased by ●**itraconazole** and ●**voriconazole**—avoid concomitant use
- Antivirals: plasma concentration of sirolimus possibly increased by ●**atazanavir** and ●**lopinavir**; plasma concentration of sirolimus increased by ●**boceprevir** (increased risk of toxicity—reduce sirolimus dose); plasma concentration of both drugs increased when sirolimus given with ●**telaprevir** (reduce dose of sirolimus)
- Calcium-channel Blockers: plasma concentration of sirolimus increased by ●**diltiazem**; plasma concentration of both drugs increased when sirolimus given with ●**verapamil**
- Cyclosporin: plasma concentration of sirolimus increased by ●**ciclosporin**
- Cytotoxics: caution with sirolimus advised by manufacturer of ●**crizotinib**
- Grapefruit Juice: plasma concentration of sirolimus increased by ●**grapefruit juice**—avoid concomitant use

Sitagliptin *see* Antidiabetics

Sodium Aurothiomalate

- ACE Inhibitors: flushing and hypotension reported when sodium aurothiomalate given with ●**ACE inhibitors**
- Penicillamine: avoidance of sodium aurothiomalate advised by manufacturer of **penicillamine** (increased risk of toxicity)

Sodium Benzoate

- Antiepileptics: effects of sodium benzoate possibly reduced by ●**valproate**
- Antipsychotics: effects of sodium benzoate possibly reduced by ●**haloperidol**
- Corticosteroids: effects of sodium benzoate possibly reduced by ●**corticosteroids**
- Probenecid: excretion of conjugate formed by sodium benzoate possibly reduced by ●**probenecid**

Sodium Bicarbonate *see* Antacids

Sodium Citrate

- Antibacterials: avoid concomitant use of sodium citrate with ●**methenamine**
- Ulcer-healing Drugs: avoidance of sodium citrate advised by manufacturer of ●**sucralfate**

Sodium Clodronate *see* Bisphosphonates

Sodium Nitroprusside *see* Vasodilator Anti-hypertensives

Sodium Oxybate

- Analgesics: effects of sodium oxybate enhanced by ●**opioid analgesics** (avoid concomitant use)
- Antidepressants: increased risk of side-effects when sodium oxybate given with ●**tricyclics**
- Antiepileptics: manufacturer of sodium oxybate advises avoid concomitant use with ●**phenobarbital**
- Antipsychotics: effects of sodium oxybate possibly enhanced by ●**antipsychotics**
- Anxiolytics and Hypnotics: effects of sodium oxybate enhanced by ●**benzodiazepines** (avoid concomitant use)

Sodium Phenylbutyrate

- Antiepileptics: effects of sodium phenylbutyrate possibly reduced by ●**valproate**
- Antipsychotics: effects of sodium phenylbutyrate possibly reduced by ●**haloperidol**
- Corticosteroids: effects of sodium phenylbutyrate possibly reduced by ●**corticosteroids**
- Probenecid: excretion of conjugate formed by sodium phenylbutyrate possibly reduced by ●**probenecid**

Sodium Stibogluconate

- Antifungals: possible increased risk of arrhythmias when sodium stibogluconate given before ●**amphotericin**—manufacturer of sodium stibogluconate advises giving 14 days apart

Sodium Valproate *see* Valproate

Sofosbuvir

- Antibacterials: manufacturer of sofosbuvir advises avoid concomitant use with ●**rifabutin** and ●**rifampicin**
- Antidepressants: manufacturer of sofosbuvir advises avoid concomitant use with ●**St John's wort**
- Antiepileptics: manufacturer of sofosbuvir advises avoid concomitant use with ●**carbamazepine**, ●**oxcarbazepine**, ●**phenobarbital** and ●**phenytoin**

Solifenacin *see* Antimuscarinics

Somatropin

- Corticosteroids: growth-promoting effect of somatropin may be inhibited by ●**corticosteroids**
- Oestrogens: increased doses of somatropin may be needed when given with ●**oestrogens** (when used as oral replacement therapy)

Sorafenib

- Antibacterials: bioavailability of sorafenib reduced by ●**neomycin**; plasma concentration of sorafenib reduced by ●**rifampicin**
- Anticoagulants: sorafenib possibly enhances anticoagulant effect of ●**coumarins**
- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)
- Antivirals: avoidance of sorafenib advised by manufacturer of ●**boceprevir**
- Cytotoxics: sorafenib possibly increases plasma concentration of ●**doxorubicin** and ●**irinotecan**; sorafenib increases plasma concentration of ●**docetaxel**

Sotalol *see* Beta-blockers

Spironolactone *see* Diuretics

Statins

- Antacids: absorption of rosuvastatin reduced by ●**antacids**
- Anti-arrhythmics: increased risk of myopathy when simvastatin given with ●**amiodarone** (see Dose under Simvastatin, p. 126); plasma concentration of atorvastatin and rosuvastatin possibly increased by ●**dronedarone**; increased risk of myopathy when simvastatin given with ●**dronedarone**
- Antibacterials: plasma concentration of atorvastatin and pravastatin increased by ●**clarithromycin**; increased risk of myopathy when simvastatin given with ●**clarithromycin**, ●**erythromycin** or ●**telithromycin** (avoid concomitant use); plasma concentration of rosuvastatin reduced by ●**erythromycin**; possible increased risk of myopathy when atorvastatin given with ●**erythromycin**; plasma concentration of pravastatin increased by ●**erythromycin**; plasma concentration of atorvastatin and simvastatin possibly reduced by ●**rifampicin**; metabolism of fluvastatin accelerated by ●**rifampicin** (reduced effect); increased risk of myopathy when statins given with ●**aprotinin** (preferably avoid concomitant use); risk of myopathy and rhabdomyolysis when statins given with ●**fusidic acid**—avoid concomitant use and for 7 days after last fusidic acid dose; possible increased risk of myopathy when pravastatin given with ●**telithromycin**; increased risk of myopathy when atorvastatin given with ●**telithromycin** (avoid concomitant use)
- Anticoagulants: atorvastatin may transiently reduce anticoagulant effect of ●**warfarin**; fluvastatin and simvastatin enhance anticoagulant effect of ●**coumarins**; rosuvastatin possibly enhances anticoagulant effect of ●**coumarins** and ●**phenindione**
- Antidepressants: plasma concentration of simvastatin reduced by ●**St John's wort**
- Antidiabetics: fluvastatin possibly increases plasma concentration of ●**glibenclamide**

Statins (continued)

- Antiepileptics: plasma concentration of simvastatin reduced by **carbamazepine** and **eslicarbazepine**—consider increasing dose of simvastatin; plasma concentration of rosuvastatin reduced by **eslicarbazepine**; combination of fluvastatin with **phenytoin** may increase plasma concentration of either drug (or both)
- Antifungals: possible increased risk of myopathy when simvastatin given with **fluconazole** or **miconazole**; possible increased risk of myopathy when atorvastatin given with **fluconazole** or **imidazoles**; plasma concentration of fluvastatin increased by **fluconazole**—possible increased risk of myopathy; increased risk of myopathy when atorvastatin given with **itraconazole**, **posaconazole** or **voriconazole**; increased risk of myopathy when simvastatin given with **itraconazole** or **posaconazole** (avoid concomitant use); increased risk of myopathy when simvastatin given with **voriconazole**
- Antivirals: increased risk of myopathy when simvastatin given with **atazanavir**, **indinavir**, **ritonavir** or **saquinavir** (avoid concomitant use); possible increased risk of myopathy when atorvastatin or pravastatin given with **atazanavir**; possible increased risk of myopathy when rosuvastatin given with **atazanavir**, **darunavir**, **fosamprenavir**, **indinavir**, **lopinavir**, **ritonavir** and **saquinavir**—manufacturer of rosuvastatin advises avoid concomitant use; plasma concentration of atorvastatin increased by **boceprevir** (reduce dose of atorvastatin); manufacturers advise avoid concomitant use of simvastatin with **boceprevir** and **telaprevir**; plasma concentration of pravastatin increased by **boceprevir**; plasma concentration of pravastatin possibly increased by **darunavir**; possible increased risk of myopathy when atorvastatin given with **darunavir**, **fosamprenavir**, **indinavir**, **lopinavir**, **ritonavir** or **saquinavir**; plasma concentration of atorvastatin, pravastatin and simvastatin reduced by **efavirenz**; plasma concentration of atorvastatin possibly reduced by **etravirine**; possible increased risk of myopathy when simvastatin given with **fosamprenavir** or **lopinavir**—avoid concomitant use; avoidance of atorvastatin advised by manufacturer of **telaprevir**; plasma concentration of simvastatin possibly increased by **tipranavir**—avoid concomitant use; increased risk of myopathy when atorvastatin given with **tipranavir** (see Dose under Atorvastatin, p. 125); plasma concentration of rosuvastatin possibly increased by **tipranavir**—manufacturer of rosuvastatin advises avoid concomitant use
- Anxiolytics and Hypnotics: atorvastatin possibly increases plasma concentration of **midazolam**
- Bosentan: plasma concentration of simvastatin reduced by **bosentan**
- Calcium-channel Blockers: possible increased risk of myopathy when simvastatin given with **amlodipine** and **diltiazem** (see Dose under Simvastatin, p. 126); plasma concentration of atorvastatin increased by **diltiazem**—possible increased risk of myopathy; increased risk of myopathy when simvastatin given with **verapamil** (see Dose under Simvastatin, p. 126)
- Cardiac Glycosides: atorvastatin possibly increases plasma concentration of **digoxin**
- Ciclosporin: increased risk of myopathy when rosuvastatin or simvastatin given with **ciclosporin** (avoid concomitant use); increased risk of myopathy when atorvastatin given with **ciclosporin** (see Dose under Atorvastatin, p. 125); increased risk of myopathy when fluvastatin or pravastatin given with **ciclosporin**
- Cobicistat: plasma concentration of atorvastatin possibly increased by **cobicistat**—manufacturer of cobicistat

Statins

- Cobicistat (continued)
 - stat advises reduce dose of atorvastatin; avoidance of simvastatin advised by manufacturer of **cobicistat**
 - Colchicine: possible increased risk of myopathy when statins given with **colchicine**
 - Cytotoxics: plasma concentration of simvastatin possibly increased by **dasatinib**; plasma concentration of simvastatin increased by **imatinib**
 - Eltrombopag: plasma concentration of rosuvastatin increased by **eltrombopag** (consider reducing dose of rosuvastatin)
 - Grapefruit Juice: plasma concentration of atorvastatin possibly increased by **grapefruit juice**; plasma concentration of simvastatin increased by **grapefruit juice**—avoid concomitant use
 - Hormone Antagonists: possible increased risk of myopathy when simvastatin given with **danazol**—avoid concomitant use
 - Lipid-regulating Drugs: possible increased risk of myopathy when simvastatin given with **bezafibrate** and **ciprofibrate** (see Dose under Simvastatin, p. 126); when given with statins reduce maximum dose of **fenofibrate**—see Dose under Fenofibrate, p. 128; increased risk of myopathy when atorvastatin, fluvastatin or pravastatin given with **gemfibrozil** (preferably avoid concomitant use); increased risk of myopathy when simvastatin given with **gemfibrozil** (avoid concomitant use); increased risk of myopathy when rosuvastatin given with **fibrates** (see Dose under Rosuvastatin, p. 126); increased risk of myopathy when statins given with **fibrates**; plasma concentration of simvastatin increased by **lomitapide** (see Dose under Simvastatin, BNF section 2.12); plasma concentration of atorvastatin increased by **lomitapide**; increased risk of myopathy when statins given with **nicotinic acid** (applies to lipid regulating doses of nicotinic acid)
 - Oestrogens: atorvastatin and rosuvastatin increase plasma concentration of **ethinylestradiol**
 - Progestogens: atorvastatin increases plasma concentration of **norethisterone**; rosuvastatin increases plasma concentration of active metabolite of **norgestimate**; rosuvastatin increases plasma concentration of **norgestrel**
 - Ranolazine: plasma concentration of simvastatin increased by **ranolazine** (see Dose under Simvastatin, BNF section 2.12)
 - Retinoids: plasma concentration of simvastatin reduced by **alitretinoin**
 - Teriflunomide: plasma concentration of rosuvastatin increased by **teriflunomide** (consider reducing dose of rosuvastatin)
 - Ticagrelor: plasma concentration of simvastatin increased by **ticagrelor** (increased risk of toxicity)
- Stavudine**
- Antivirals: increased risk of side-effects when stavudine given with **didanosine**; increased risk of toxicity when stavudine given with **ribavirin**; effects of stavudine possibly inhibited by **zidovudine** (manufacturers advise avoid concomitant use)
 - Cytotoxics: effects of stavudine possibly inhibited by **doxorubicin**; increased risk of toxicity when stavudine given with **hydroxycarbamide**—avoid concomitant use
 - Orlistat: absorption of stavudine possibly reduced by **orlistat**
- Stiripentol**
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIs** and **tricyclics** (convulsive threshold lowered)

Stiripentol (*continued*)

- Antiepileptics: stiripentol increases plasma concentration of ●**carbamazepine**, ●**phenobarbital** and ●**phenytoin**
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by ●**mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ●**antipsychotics** (convulsive threshold lowered)
- Anxiolytics and Hypnotics: stiripentol increases plasma concentration of ●**clobazam**
- Orlistat: possible increased risk of convulsions when antiepileptics given with ●**orlistat**

Streptomycin *see* Aminoglycosides

Strontium Ranelate

Antibacterials: strontium ranelate reduces absorption of ●**quinolones** and ●**tetracyclines** (manufacturer of strontium ranelate advises avoid concomitant use)

Sucralfate

Antibacterials: sucralfate reduces absorption of ●**ciprofloxacin**, ●**levofloxacin**, ●**moxifloxacin**, ●**ofloxacin** and ●**tetracyclines**; sucralfate reduces absorption of ●**norfloxacin** (give at least 2 hours apart)

- Anticoagulants: sucralfate possibly reduces absorption of ●**coumarins** (reduced anticoagulant effect)
- Antiepileptics: sucralfate reduces absorption of ●**phenytoin**

Antipsychotics: sucralfate reduces absorption of ●**sulpiride**

Cardiac Glycosides: sucralfate possibly reduces absorption of ●**cardiac glycosides**

Potassium Salts: manufacturer of sucralfate advises avoid concomitant use with ●**potassium citrate**

Sodium Citrate: manufacturer of sucralfate advises avoid concomitant use with ●**sodium citrate**

Theophylline: sucralfate possibly reduces absorption of ●**theophylline** (give at least 2 hours apart)

Thyroid Hormones: sucralfate reduces absorption of ●**levothyroxine**

Ulcer-healing Drugs: sucralfate possibly reduces absorption of ●**lansoprazole**

Sugammadex

Antibacterials: response to sugammadex possibly reduced by ●**fusidic acid**

Progestogens: sugammadex possibly reduces plasma concentration of ●**progestogens**—manufacturer of sugammadex advises additional contraceptive precautions

Sulfadiazine *see* Sulfonamides

Sulfadoxine *see* Sulfonamides

Sulfamethoxazole *see* Sulfonamides

Sulfasalazine *see* Aminosalicylates

Sulfipyrazone

Analgesics: effects of sulfipyrazone antagonised by ●**aspirin**

Antibacterials: sulfipyrazone reduces excretion of ●**nitrofurantoin** (increased risk of toxicity); sulfipyrazone reduces excretion of ●**penicillins**; effects of sulfipyrazone antagonised by ●**pyrazinamide**

- Anticoagulants: increased risk of bleeding when sulfipyrazone given with ●**apixaban**; sulfipyrazone enhances anticoagulant effect of ●**coumarins**; possible increased risk of bleeding when sulfipyrazone given with ●**dabigatran**

- Antidiabetics: sulfipyrazone enhances effects of ●**sulfonylureas**

- Antiepileptics: sulfipyrazone increases plasma concentration of ●**phenytoin**

Calcium-channel Blockers: sulfipyrazone reduces plasma concentration of ●**verapamil**

- Ciclosporin: sulfipyrazone reduces plasma concentration of ●**ciclosporin**

Theophylline: sulfipyrazone reduces plasma concentration of ●**theophylline**

Sulfonamides

Anaesthetics, General: sulfonamides enhance effects of ●**thiopental**

- Anaesthetics, Local: effects of sulfonamides possibly inhibited by ●**chlorprocaine** (manufacturer of chlorprocaine advises avoid concomitant use); increased risk of methaemoglobinemia when sulfonamides given with ●**prilocaine**

Anti-arrhythmics: possible increased risk of ventricular arrhythmias when sulfamethoxazole (as co-trimoxazole) given with ●**amiodarone**—manufacturer of amiodarone advises avoid concomitant use of co-trimoxazole

- Antibacterials: increased risk of crystalluria when sulfonamides given with ●**methenamine**

- Anticoagulants: sulfonamides enhance anticoagulant effect of ●**coumarins**; sulfonamides possibly inhibit metabolism of ●**phenindione**

Antidiabetics: sulfonamides rarely enhance the effects of ●**sulfonylureas**

Antiepileptics: sulfonamides possibly increase plasma concentration of ●**phenytoin**

- Antimalarials: increased antifolate effect when sulfonamides given with ●**pyrimethamine**

- Antipsychotics: avoid concomitant use of sulfonamides with ●**clozapine** (increased risk of agranulocytosis)

- Azathioprine: increased risk of haematological toxicity when sulfamethoxazole (as co-trimoxazole) given with ●**azathioprine**

- Ciclosporin: increased risk of nephrotoxicity when sulfonamides given with ●**ciclosporin**; sulfadiazine possibly reduces plasma concentration of ●**ciclosporin**

- Cytotoxics: increased risk of haematological toxicity when sulfamethoxazole (as co-trimoxazole) given with ●**mercaptopurine** or ●**methotrexate**; sulfonamides increase risk of ●**methotrexate** toxicity

Potassium Aminobenzoate: effects of sulfonamides inhibited by ●**potassium aminobenzoate**

Vaccines: antibacterials inactivate ●**oral typhoid vaccine**—see p. 626

Sulfonylureas *see* Antidiabetics

Sulindac *see* NSAIDs

Sulpiride *see* Antipsychotics

Sumatriptan *see* 5HT₁-receptor Agonists (under HT)

Sunitinib

Antibacterials: metabolism of sunitinib accelerated by ●**rifampicin** (reduced plasma concentration)

- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)

- Antivirals: avoidance of sunitinib advised by manufacturer of ●**boceprevir**

Suxamethonium *see* Muscle Relaxants

Sympathomimetics

- Adrenergic Neurone Blockers: ephedrine, isometheptene, metaraminol, methylphenidate, noradrenaline (norepinephrine), oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline antagonise hypotensive effect of ●**adrenergic neurone blockers**; dexamfetamine and lisdexanfetanamine antagonise hypotensive effect of ●**guanethidine**

Alcohol: effects of methylphenidate possibly enhanced by ●**alcohol**

Alpha₂-adrenoceptor Stimulants: avoidance of sympathomimetics advised by manufacturer of ●**apraclonidine**

- Alpha-blockers: avoid concomitant use of adrenaline (epinephrine) or dopamine with ●**tolazoline**

- Anaesthetics, General: avoidance of sympathomimetics advised by manufacturer of ●**isoflurane** (risk of ventricular arrhythmias); increased risk of hypertension when methylphenidate given with ●**volatile liquid general anaesthetics**; increased risk of arrhythmias when adrenaline (epinephrine) or

Sympathomimetics

- Anaesthetics, General (*continued*)
noradrenaline (norepinephrine) given with **●volatile liquid general anaesthetics**
- Antacids: absorption of pseudoephedrine possibly increased by **●aluminium hydroxide**
- Anticoagulants: methylphenidate possibly enhances anticoagulant effect of **●coumarins**
- Antidepressants: risk of hypertensive crisis when adrenaline (epinephrine), dobutamine, dopamine, methoxamine, noradrenaline (norepinephrine) or xylometazoline given with **●MAOIs**; risk of hypertensive crisis when dexamfetamine, ephedrine, isometheptene, lisdexafetamine, metaraminol, methylphenidate, phenylephrine or pseudoephedrine given with **●MAOIs**, avoid dexamfetamine, ephedrine, isometheptene, lisdexafetamine, metaraminol, methylphenidate, phenylephrine or pseudoephedrine for at least 2 weeks after stopping MAOIs; risk of hypertensive crisis when oxymetazoline given with **●MAOIs**, some manufacturers advise avoid oxymetazoline for at least 2 weeks after stopping MAOIs; risk of hypertensive crisis when sympathomimetics given with **●moclobemide**; methylphenidate possibly inhibits metabolism of **SSRIs** and **tricyclics**; increased risk of hypertension and arrhythmias when adrenaline (epinephrine) given with **●tricyclics** (but local anaesthetics with adrenaline appear to be safe); increased risk of hypertension and arrhythmias when noradrenaline (norepinephrine) or phenylephrine given with **●tricyclics**
- Antiepileptics: methylphenidate possibly increases plasma concentration of **phenobarbital**; methylphenidate increases plasma concentration of **phenytoin**
- Antipsychotics: hypertensive effect of sympathomimetics antagonised by **antipsychotics**; effects of lisdexafetamine possibly reduced by **chlorpromazine**; dexamfetamine possibly antagonises antipsychotic effects of **chlorpromazine**; methylphenidate possibly increases side-effects of **risperidone**
- Antivirals: plasma concentration of dexamfetamine possibly increased by **ritonavir**
- Beta-blockers: increased risk of severe hypertension and bradycardia when adrenaline (epinephrine) given with non-cardioselective **●beta-blockers**, also response to adrenaline (epinephrine) may be reduced; increased risk of severe hypertension and bradycardia when dobutamine given with non-cardioselective **●beta-blockers**; possible increased risk of severe hypertension and bradycardia when noradrenaline (norepinephrine) given with non-cardioselective **●beta-blockers**
- Clonidine: possible risk of hypertension when adrenaline (epinephrine) or noradrenaline (norepinephrine) given with **clonidine**; serious adverse events reported with concomitant use of methylphenidate and **●clonidine** (causality not established)
- Corticosteroids: ephedrine accelerates metabolism of **dexamethasone**
- Dopaminergics: risk of toxicity when isometheptene given with **●bromocriptine**; effects of adrenaline (epinephrine), dobutamine, dopamine and noradrenaline (norepinephrine) possibly enhanced by **entacapone**; avoid concomitant use of sympathomimetics with **●rasagiline**; avoidance of sympathomimetics advised by manufacturer of **selegiline**; risk of hypertensive crisis when dopamine given with **●selegiline**
- Doxapram: increased risk of hypertension when sympathomimetics given with **doxapram**
- Ergot Alkaloids: increased risk of ergotism when sympathomimetics given with **ergotamine**
- Oxytocin: risk of hypertension when vasoconstrictor sympathomimetics given with **oxytocin** (due to enhanced vasopressor effect)

Sympathomimetics (*continued*)

- Sympathomimetics: effects of adrenaline (epinephrine) possibly enhanced by **●dopexamine**; dopexamine possibly enhances effects of **●noradrenaline (norepinephrine)**
- Theophylline: avoidance of ephedrine in children advised by manufacturer of **theophylline**
- Sympathomimetics, Beta₂**
- Antivirals: avoidance of salmeterol advised by manufacturer of **lopinavir**, **ritonavir** and **tipranavir**; avoidance of salmeterol advised by manufacturer of **●telaprevir** (risk of ventricular arrhythmias)
- Atomoxetine: Increased risk of cardiovascular side-effects when *parenteral* salbutamol given with **atomoxetine**
- Cardiac Glycosides: salbutamol possibly reduces plasma concentration of **digoxin**
- Cobicistat: avoidance of salmeterol advised by manufacturer of **cobicistat**
- Corticosteroids: increased risk of hypokalaemia when high doses of beta₂ sympathomimetics given with **corticosteroids**—see Hypokalaemia, p. 136
- Diuretics: increased risk of hypokalaemia when high doses of beta₂ sympathomimetics given with **aceta-zolamide**, **loop diuretics** or **thiazides and related diuretics**—see Hypokalaemia, p. 136
- Methyldopa: acute hypotension reported when *infusion* of salbutamol given with **●methyldopa**
- Muscle Relaxants: bambuterol enhances effects of **suxamethonium**
- Theophylline: increased risk of hypokalaemia when high doses of beta₂ sympathomimetics given with **theophylline**—see Hypokalaemia, p. 136

Tacrolimus

- Note** Interactions do not generally apply to tacrolimus used topically; risk of facial flushing and skin irritation with alcohol consumption (p. 580) does not apply to tacrolimus taken systemically
- Analgesics: possible increased risk of nephrotoxicity when tacrolimus given with **NSAIDs**; increased risk of nephrotoxicity when tacrolimus given with **●ibuprofen**
 - Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when tacrolimus given with **angiotensin-II receptor antagonists**
 - Anti-arrhythmics: caution with tacrolimus advised by manufacturer of **dronedarone**
 - Antibacterials: plasma concentration of tacrolimus increased by **●clarithromycin** and **●erythromycin**; plasma concentration of tacrolimus possibly reduced by **rifabutin**; plasma concentration of tacrolimus reduced by **●rifampicin**; increased risk of nephrotoxicity when tacrolimus given with **●amino-glycosides**; plasma concentration of tacrolimus possibly increased by **●chloramphenicol** and **●telithromycin**; possible increased risk of nephrotoxicity when tacrolimus given with **vancomycin**
 - Anticoagulants: tacrolimus possibly increases plasma concentration of **●dabigatran**—manufacturer of dabigatran advises avoid concomitant use
 - Antidepressants: plasma concentration of tacrolimus reduced by **●St John's wort**—avoid concomitant use
 - Antiepileptics: plasma concentration of tacrolimus reduced by **●phenobarbital**; plasma concentration of tacrolimus reduced by **phenytoin**, also plasma concentration of phenytoin possibly increased
 - Antifungals: plasma concentration of tacrolimus possibly increased by **●miconazole oral gel**; increased risk of nephrotoxicity when tacrolimus given with **●amphotericin**; plasma concentration of tacrolimus increased by **●fluconazole**, **●itraconazole**, **●posaconazole** and **●voriconazole** (consider reducing dose of tacrolimus); plasma concentration of tacrolimus reduced by **●casprofungin**

Tacrolimus (*continued*)

- Antipsychotics: avoidance of tacrolimus advised by manufacturer of **droperidol** (risk of ventricular arrhythmias)
- Antivirals: possible increased risk of nephrotoxicity when tacrolimus given with **aciclovir** or **ganciclovir**; plasma concentration of tacrolimus possibly increased by **atazanavir** and **ritonavir**; plasma concentration of tacrolimus increased by **boceprevir** (reduce dose of tacrolimus); plasma concentration of tacrolimus possibly affected by **efavirenz**; plasma concentration of tacrolimus increased by **fosamprenavir**; plasma concentration of tacrolimus increased by **saguinavir** (consider reducing dose of tacrolimus); plasma concentration of both drugs increased when tacrolimus given with **telaprevir** (reduce dose of tacrolimus)
- Calcium-channel Blockers: plasma concentration of tacrolimus possibly increased by **felodipine**, **nicardipine** and **verapamil**; plasma concentration of tacrolimus increased by **diltiazem** and **nifedipine**
- Ciclosporin: tacrolimus increases plasma concentration of **ciclosporin** (increased risk of nephrotoxicity)—avoid concomitant use
- Colestilan: manufacturer of colestilan advises give tacrolimus at least 1 hour before or 3 hours after **colestilan**
- Cytotoxics: tacrolimus possibly increases the plasma concentration of **afatinib**—manufacturer of afatinib advises separating administration of tacrolimus by 6 to 12 hours; caution with tacrolimus advised by manufacturer of **crizotinib**; plasma concentration of tacrolimus increased by **imatinib**
- Diuretics: increased risk of hyperkalaemia when tacrolimus given with **potassium-sparing diuretics** and **aldosterone antagonists**
- Grapefruit Juice: plasma concentration of tacrolimus increased by **grapefruit juice**
- Hormone Antagonists: plasma concentration of tacrolimus possibly increased by **danazol**
- Mifamurtide: avoidance of tacrolimus advised by manufacturer of **mifamurtide**
- Oestrogens: plasma concentration of tacrolimus possibly increased by **ethinylestradiol**
- Potassium Salts: increased risk of hyperkalaemia when tacrolimus given with **potassium salts**
- Ranolazine: plasma concentration of tacrolimus increased by **ranolazine**
- Sevelamer: plasma concentration of tacrolimus possibly reduced by **sevelamer**
- Ulcer-healing Drugs: plasma concentration of tacrolimus possibly increased by **omeprazole**

Tadalafil

- Alpha-blockers: enhanced hypotensive effect when tadalafil given with **doxazosin**—manufacturer of tadalafil advises avoid concomitant use; enhanced hypotensive effect when tadalafil given with **alpha-blockers**—see also under Phosphodiesterase type-5 inhibitors, BNF section 7.4.5
- Anti-arrhythmics: avoidance of tadalafil advised by manufacturer of **disopyramide** (risk of ventricular arrhythmias)
- Antibacterials: plasma concentration of tadalafil possibly increased by **clarithromycin** and **erythromycin**; plasma concentration of tadalafil reduced by **rifampicin**—manufacturer of tadalafil advises avoid concomitant use
- Antifungals: plasma concentration of tadalafil possibly increased by **itraconazole**
- Antivirals: plasma concentration of tadalafil possibly increased by **fosamprenavir** and **indinavir**; plasma concentration of tadalafil increased by **ritonavir**—manufacturer of tadalafil advises avoid concomitant use; increased risk of ventricular arrhythmias when tadalafil given with **saguinavir**—avoid concomitant use; avoidance of high doses of tadalafil advised by

Tadalafil**Antivirals** (*continued*)

- manufacturer of **telaprevir**—consult product literature
- Bosentan: plasma concentration of tadalafil reduced by **bosentan**
- Cobicistat: plasma concentration of tadalafil possibly increased by **cobicistat**—manufacturer of cobicistat advises reduce dose of tadalafil (consult cobicistat product literature)
- Dapoxetine: avoidance of tadalafil advised by manufacturer of **dapoxetine**
- Grapefruit Juice: plasma concentration of tadalafil possibly increased by **grapefruit juice**
- Nicorandil: tadalafil significantly enhances hypotensive effect of **nicorandil** (avoid concomitant use)
- Nitrates: tadalafil significantly enhances hypotensive effect of **nitrates** (avoid concomitant use)

Tamoxifen

- Antibacterials: metabolism of tamoxifen accelerated by **rifampicin** (reduced plasma concentration)
- Anticoagulants: tamoxifen enhances anticoagulant effect of **coumarins**
- Antidepressants: metabolism of tamoxifen to active metabolite possibly inhibited by **fluoxetine** and **paroxetine** (avoid concomitant use)
- Antipsychotics: avoidance of tamoxifen advised by manufacturer of **droperidol** (risk of ventricular arrhythmias)
- Bupropion: metabolism of tamoxifen to active metabolite possibly inhibited by **bupropion** (avoid concomitant use)
- Cinacalcet: metabolism of tamoxifen to active metabolite possibly inhibited by **cinacalcet** (avoid concomitant use)

Tamsulosin see Alpha-blockers

Tapentadol see Opioid Analgesics

Taxanes see Cabazitaxel, Docetaxel, and Paclitaxel

Tegafur see Fluorouracil

Teicoplanin

Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Telaprevir

- Alpha-blockers: manufacturer of telaprevir advises avoid concomitant use with **alfuzosin**
- Analgesics: manufacturer of telaprevir advises caution with **methadone** (risk of ventricular arrhythmias)
- Anti-arrhythmics: manufacturer of telaprevir advises avoid concomitant use with **amiodarone** and **disopyramide** (risk of ventricular arrhythmias); manufacturer of telaprevir advises caution with **alpha-blockers** (risk of ventricular arrhythmias); manufacturer of telaprevir advises caution with **intravenous lidocaine**
- Antibacterials: plasma concentration of both drugs possibly increased when telaprevir given with **clarithromycin**, **erythromycin** and **telithromycin** (increased risk of ventricular arrhythmias); manufacturer of telaprevir advises avoid concomitant use with **rifabutin**; plasma concentration of telaprevir significantly reduced by **rifampicin**—avoid concomitant use
- Anticoagulants: telaprevir possibly affects plasma concentration of **warfarin**; telaprevir possibly increases plasma concentration of **dabigatran**
- Antidepressants: telaprevir possibly increases plasma concentration of **trazodone**; manufacturer of telaprevir advises avoid concomitant use with **St John's wort**
- Antiepileptics: manufacturer of telaprevir advises avoid concomitant use with **carbamazepine**, **phenobarbital** and **phenytoin**
- Antifungals: telaprevir possibly increases plasma concentration of **itraconazole**; telaprevir possibly increases plasma concentration of

Telaprevir

- Antifungals (*continued*)
 - **posaconazole** (increased risk of ventricular arrhythmias); telaprevir possibly affects plasma concentration of ● **voriconazole** (possible increased risk of ventricular arrhythmias)
- Antipsychotics: manufacturer of telaprevir advises avoid concomitant use with ● **pimozide**; telaprevir possibly increases plasma concentration of ● **quetiapine**—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: plasma concentration of telaprevir possibly reduced by ● **atazanavir**, also plasma concentration of atazanavir possibly increased; avoid concomitant use of telaprevir with ● **darunavir**; plasma concentration of telaprevir reduced by ● **efavirenz**—increase dose of telaprevir; manufacturers advise avoid concomitant use of telaprevir with ● **fosamprenavir** and ● **lopinavir**; telaprevir increases plasma concentration of ● **maraviroc** (consider reducing dose of maraviroc); plasma concentration of telaprevir possibly reduced by ● **ritonavir**; telaprevir increases plasma concentration of ● **tenofovir**
- Anxiolytics and Hypnotics: telaprevir possibly increases plasma concentration of ● **midazolam** (risk of prolonged sedation—avoid concomitant use of oral midazolam)
- Beta-blockers: manufacturer of telaprevir advises avoid concomitant use with ● **sotalol** (risk of ventricular arrhythmias)
- Bosentan: plasma concentration of telaprevir possibly reduced by ● **bosentan**, also plasma concentration of bosentan possibly increased
- Calcium-channel Blockers: telaprevir increases plasma concentration of ● **amlodipine** (consider reducing dose of amlodipine); manufacturer of telaprevir advises caution with ● **diltiazem**, ● **felodipine**, ● **nicardipine**, ● **nifedipine** and ● **verapamil**
- Cardiac Glycosides: telaprevir increases plasma concentration of ● **digoxin**
- Ciclosporin: plasma concentration of both drugs increased when telaprevir given with ● **ciclosporin** (reduce dose of ciclosporin)
- Cilostazol: telaprevir possibly increases plasma concentration of ● **cilostazol** (see Dose under Cilostazol, BNF section 2.6.4)
- Colchicine: telaprevir possibly increases risk of ● **colchicine** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: telaprevir possibly increases plasma concentration of inhaled and intranasal ● **budesonide** and ● **fluticasone**; plasma concentration of telaprevir possibly reduced by ● **dexamethasone**
- Cytotoxics: telaprevir possibly increases the plasma concentration of ● **bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; manufacturer of ruxolitinib advises dose reduction when telaprevir given with ● **ruxolitinib**—consult ruxolitinib product literature
- Domperidone: telaprevir possibly increases plasma concentration of ● **domperidone**—manufacturer of telaprevir advises avoid concomitant use
- Ergot Alkaloids: manufacturer of telaprevir advises avoid concomitant use with ● **ergot alkaloids**
- Lipid-regulating Drugs: manufacturer of telaprevir advises avoid concomitant use with ● **atorvastatin**; manufacturers advise avoid concomitant use of telaprevir with ● **simvastatin**; avoidance of telaprevir advised by manufacturer of ● **lomitapide** (plasma concentration of lomitapide possibly increased)
- Oestrogens: telaprevir possibly reduces plasma concentration of ● **ethinylestradiol**—manufacturer of telaprevir advises additional contraceptive precautions

Telaprevir (*continued*)

- Sildenafil: manufacturer of telaprevir advises avoid concomitant use with ● **sildenafil**
- Sirolimus: plasma concentration of both drugs increased when telaprevir given with ● **sirolimus** (reduce dose of sirolimus)
- Sympathomimetics, Beta₂: manufacturer of telaprevir advises avoid concomitant use with ● **salmeterol** (risk of ventricular arrhythmias)
- Tacrolimus: plasma concentration of both drugs increased when telaprevir given with ● **tacrolimus** (reduce dose of tacrolimus)
- Tadalafil: manufacturer of telaprevir advises avoid concomitant use with high doses of ● **tadalafil**—consult product literature
- Vardenafil: manufacturer of telaprevir advises avoid concomitant use with ● **vardenafil**

Telbivudine

- Interferons: increased risk of peripheral neuropathy when telbivudine given with ● **interferon alfa**

Telithromycin

- Analgesics: possible increased risk of ventricular arrhythmias when telithromycin given with ● **methadone**; telithromycin inhibits the metabolism of ● **oxycodone**
- Anti-arrhythmics: possible increased risk of ventricular arrhythmias when telithromycin given with ● **amiodarone** and ● **disopyramide**; increased risk of ventricular arrhythmias when telithromycin given with ● **dronedaron**—avoid concomitant use
- Antibacterials: possible increased risk of ventricular arrhythmias when telithromycin given with ● **moxi-floxacin**; plasma concentration of telithromycin reduced by ● **rifampicin** (avoid during and for 2 weeks after rifampicin)
- Antidepressants: possible increased risk of ventricular arrhythmias when telithromycin given with ● **citalopram** and ● **tricyclics**; plasma concentration of telithromycin reduced by ● **St John's wort** (avoid during and for 2 weeks after St John's wort)
- Antiepileptics: plasma concentration of telithromycin reduced by ● **carbamazepine**, ● **phenobarbital** and ● **phenytoin** (avoid during and for 2 weeks after carbamazepine, phenobarbital and phenytoin)
- Antimuscarinics: manufacturer of fesoterodine advises dose reduction when telithromycin given with ● **fesoterodine**—consult fesoterodine product literature
- Antipsychotics: possible increased risk of ventricular arrhythmias when telithromycin given with ● **chlorpromazine**; increased risk of ventricular arrhythmias when telithromycin given with ● **pimozide**—avoid concomitant use; telithromycin possibly increases plasma concentration of ● **quetiapine**
- Antivirals: manufacturer of telithromycin advises avoid concomitant use with ● **atazanavir**, ● **fosamprenavir**, ● **indinavir**, ● **lopinavir**, ● **ritonavir** and ● **tipranavir** in severe renal and hepatic impairment; telithromycin possibly increases plasma concentration of ● **maraviroc** (consider reducing dose of maraviroc); manufacturer of telithromycin advises avoid concomitant use with ● **saquinavir** (risk of ventricular arrhythmias); plasma concentration of both drugs possibly increased when telithromycin given with ● **telaprevir** (increased risk of ventricular arrhythmias)
- Anxiolytics and Hypnotics: telithromycin inhibits metabolism of ● **midazolam** (increased plasma concentration with increased sedation)
- Aprepitant: telithromycin possibly increases plasma concentration of ● **aprepitant**
- Calcium-channel Blockers: telithromycin possibly inhibits metabolism of ● **calcium-channel blockers** (increased risk of side-effects)
- Cardiac Glycosides: telithromycin possibly increases plasma concentration of ● **digoxin**

Telithromycin (*continued*)

- Cyclosporin: telithromycin possibly increases plasma concentration of **cyclosporin**
- Colchicine: telithromycin possibly increases risk of **colchicine** toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Cytotoxics: telithromycin possibly increases plasma concentration of **axitinib** (reduce dose of axitinib—consult axitinib product literature); telithromycin possibly increases the plasma concentration of **bosutinib** and **cabazitaxel**—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; telithromycin possibly increases plasma concentration of **crizotinib** and **everolimus**—manufacturer of crizotinib and everolimus advises avoid concomitant use; avoidance of telithromycin advised by manufacturer of **lapatinib** and **nilotinib**; telithromycin possibly increases plasma concentration of **pazopanib** (reduce dose of pazopanib); manufacturer of ruxolitinib advises dose reduction when telithromycin given with **ruxolitinib**—consult ruxolitinib product literature
- Dapoxetine: avoidance of telithromycin advised by manufacturer of **dapoxetine** (increased risk of toxicity)
- Diuretics: telithromycin increases plasma concentration of **eplerenone**—avoid concomitant use
- Ergot Alkaloids: increased risk of ergotism when telithromycin given with **ergotamine**—avoid concomitant use
- Ivabradine: telithromycin possibly increases plasma concentration of **ivabradine**—avoid concomitant use
- Ivacaftor: telithromycin possibly increases plasma concentration of **ivacaftor** (see Dose under Ivacaftor, p. 165)
- Lipid-regulating Drugs: increased risk of myopathy when telithromycin given with **atorvastatin** or **simvastatin** (avoid concomitant use); possible increased risk of myopathy when telithromycin given with **pravastatin**; avoidance of telithromycin advised by manufacturer of **lomitapide** (plasma concentration of lomitapide possibly increased)
- Pentamidine Isetionate: possible increased risk of ventricular arrhythmias when telithromycin given with parenteral **pentamidine isetionate**
- Ranolazine: telithromycin possibly increases plasma concentration of **ranolazine**—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: telithromycin possibly increases plasma concentration of **sildenafil**—reduce initial dose of sildenafil
- Sirolimus: telithromycin increases plasma concentration of **sirolimus**—avoid concomitant use
- Tacrolimus: telithromycin possibly increases plasma concentration of **tacrolimus**
- Ulipristal: avoidance of telithromycin advised by manufacturer of **ulipristal**
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Telmisartan *see* Angiotensin-II Receptor Antagonists

Temazepam *see* Anxiolytics and Hypnotics

Temocillin *see* Penicillins

Temporfin

- Cytotoxics: increased skin photosensitivity when temporfin given with **topical 5-fluorouracil**

Temozolomide

Antiepileptics: plasma concentration of temozolomide increased by **valproate**

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Temsirolimus

Note The main active metabolite of temsirolimus is sirolimus—*see also* interactions of sirolimus and consult product literature

- Antibacterials: plasma concentration of active metabolite of temsirolimus reduced by **rifampicin**—avoid concomitant use
- Antifungals: manufacturer of temsirolimus advises avoid concomitant use with **itraconazole** (plasma concentration of temsirolimus possibly increased)
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Tenofovir

- Antivirals: manufacturer of tenofovir advises avoid concomitant use with **adefovir**; tenofovir reduces plasma concentration of **atazanavir**, also plasma concentration of tenofovir possibly increased; manufacturers advise avoid concomitant use of tenofovir with **cidofovir**; tenofovir increases plasma concentration of **didanosine** (increased risk of toxicity)—avoid concomitant use; plasma concentration of tenofovir increased by **lopinavir** and **telaprevir**
- Orlistat: absorption of tenofovir possibly reduced by **orlistat**

Tenoxicam *see* NSAIDs

Terazosin *see* Alpha-blockers

Terbinafine

- Antibacterials: plasma concentration of terbinafine reduced by **rifampicin**
- Antidepressants: terbinafine possibly increases plasma concentration of **paroxetine** and **tricyclics**
- Antifungals: terbinafine increases plasma concentration of **fluconazole**
- Cyclosporin: terbinafine possibly reduces plasma concentration of **cyclosporin**
- Oestrogens: occasional reports of breakthrough bleeding when terbinafine given with **oestrogens** (when used for contraception)
- Progestogens: occasional reports of breakthrough bleeding when terbinafine given with **progestogens** (when used for contraception)
- Ulcer-healing Drugs: plasma concentration of terbinafine increased by **cimetidine**

Terbutaline *see* Sympathomimetics, Beta₂

Teriflunomide

- Antibacterials: teriflunomide increases plasma concentration of **cefaclor**; plasma concentration of teriflunomide reduced by **rifampicin**
- Antidiabetics: teriflunomide increases plasma concentration of **repaglinide**
- Lipid-regulating Drugs: the effect of teriflunomide is significantly decreased by **colestyramine** (enhanced elimination)—avoid unless drug elimination desired; teriflunomide increases plasma concentration of **rosuvastatin** (consider reducing dose of rosuvastatin)
- Oestrogens: teriflunomide increases plasma concentration of **ethinylestradiol**
- Progestogens: teriflunomide increases plasma concentration of **levonorgestrel**
- Vaccines: avoid concomitant use of teriflunomide with live **vaccines** (see p. 604)

Testolactone

- Anticoagulants: testolactone enhances anticoagulant effect of **coumarins** and **phenindione**

Testosterone

- Anticoagulants: testosterone enhances anticoagulant effect of **coumarins** and **phenindione**
- Antidiabetics: testosterone possibly enhances hypoglycaemic effect of **antidiabetics**

Tetrabenazine

- Antidepressants: risk of CNS toxicity when tetrabenazine given with **MAOIs** (avoid tetrabenazine for 2 weeks after MAOIs)

Tetrabenazine (*continued*)

Antipsychotics: increased risk of extrapyramidal side-effects when tetrabenazine given with **antipsychotics**

Dopaminergics: increased risk of extrapyramidal side-effects when tetrabenazine given with **amantadine**

Metoclopramide: increased risk of extrapyramidal side-effects when tetrabenazine given with **metoclopramide**

Tetracosactide *see* Corticosteroids

Tetracycline *see* Tetracyclines

Tetracyclines

ACE Inhibitors: absorption of tetracyclines reduced by **quinapril** tablets (quinapril tablets contain magnesium carbonate)

Adsorbents: absorption of tetracyclines possibly reduced by **kaolin**

Antacids: absorption of tetracyclines reduced by **antacids**

Antibacterials: plasma concentration of doxycycline reduced by **rifampicin**—consider increasing dose of doxycycline; tetracyclines possibly antagonise effects of **penicillins**

- Anticoagulants: tetracyclines possibly enhance anticoagulant effect of **coumarins** and **phenindione**

Antidiabetics: tetracyclines possibly enhance hypoglycaemic effect of **sulfonylureas**

Antiepileptics: metabolism of doxycycline accelerated by **carbamazepine** (reduced effect); metabolism of doxycycline accelerated by **phenobarbital** and **phenytoin** (reduced plasma concentration)

Atovaquone: tetracycline reduces plasma concentration of **atovaquone**

Calcium Salts: absorption of tetracycline reduced by **calcium salts**

Cytotoxics: doxycycline or tetracycline increase risk of **methotrexate** toxicity

Dairy Products: absorption of tetracyclines (except doxycycline and minocycline) reduced by **dairy products**

Diuretics: manufacturer of lymecycline advises avoid concomitant use with **diuretics**

Ergot Alkaloids: increased risk of ergotism when tetracyclines given with **ergotamine**

Iron: absorption of tetracyclines reduced by **oral iron**, also absorption of **oral iron** reduced by tetracyclines

Lipid-regulating Drugs: absorption of tetracycline possibly reduced by **colestipol** and **colestyramine**

- Retinoids: possible increased risk of benign intracranial hypertension when tetracyclines given with **retinoids** (avoid concomitant use)

Strontium Ranelate: absorption of tetracyclines reduced by **strontium ranelate** (manufacturer of strontium ranelate advises avoid concomitant use)

Ulcer-healing Drugs: absorption of tetracyclines reduced by **sucralfate** and **tripotassium dicitrate-bismuthate**

Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Zinc: absorption of tetracyclines reduced by **zinc**, also absorption of zinc reduced by tetracyclines

Theophylline

Allopurinol: plasma concentration of theophylline possibly increased by **allopurinol**

Anaesthetics, General: increased risk of convulsions when theophylline given with **ketamine**

Anti-arrhythmics: theophylline antagonises anti-arrhythmic effect of **adenosine**—manufacturer of adenosine advises avoid theophylline for 24 hours before adenosine; plasma concentration of theophylline increased by **propafenone**

- Antibacterials: plasma concentration of theophylline possibly increased by **clarithromycin** and **isoniazid**; plasma concentration of theophylline increased by **erythromycin** (also theophylline may reduce absorption of **oral erythromycin**); plasma concentra-

Theophylline• Antibacterials (*continued*)

tion of theophylline increased by **ciprofloxacin** and **norfloxacin**; metabolism of theophylline accelerated by **rifampicin** (reduced plasma concentration); possible increased risk of convulsions when theophylline given with **quinolones**

- Antidepressants: plasma concentration of theophylline increased by **fluvoxamine** (concomitant use should usually be avoided, but where not possible halve theophylline dose and monitor plasma-theophylline concentration); plasma concentration of theophylline possibly reduced by **St John's wort**

- Antiepileptics: metabolism of theophylline accelerated by **carbamazepine** and **phenobarbital** (reduced effect); plasma concentration of both drugs reduced when theophylline given with **phenytoin**

- Antifungals: plasma concentration of theophylline possibly increased by **fluconazole**

- Antivirals: plasma concentration of theophylline possibly increased by **aciclovir**; metabolism of theophylline accelerated by **ritonavir** (reduced plasma concentration)

Anxiolytics and Hypnotics: theophylline possibly reduces effects of **benzodiazepines**

Caffeine citrate: avoidance of theophylline advised by manufacturer of **caffeine citrate**

- Calcium-channel Blockers: plasma concentration of theophylline possibly increased by **calcium-channel blockers** (enhanced effect); plasma concentration of theophylline increased by **diltiazem**; plasma concentration of theophylline increased by **verapamil** (enhanced effect)

Corticosteroids: increased risk of hypokalaemia when theophylline given with **corticosteroids**

Cytotoxics: plasma concentration of theophylline possibly increased by **methotrexate**

- Deferasirox: plasma concentration of theophylline increased by **deferasirox** (consider reducing dose of theophylline)

Disulfiram: metabolism of theophylline inhibited by **disulfiram** (increased risk of toxicity)

Diuretics: increased risk of hypokalaemia when theophylline given with **acetazolamide**, **loop diuretics** or **thiazides and related diuretics**

Doxapram: increased CNS stimulation when theophylline given with **doxapram**

- Interferons: metabolism of theophylline inhibited by **interferon alfa** (consider reducing dose of theophylline)

Leukotriene Receptor Antagonists: plasma concentration of theophylline possibly increased by **zafirlukast**, also plasma concentration of zafirlukast reduced

Lithium: theophylline increases excretion of **lithium** (reduced plasma concentration)

Oestrogens: plasma concentration of theophylline increased by **oestrogens** (consider reducing dose of theophylline)

Pentoxifylline: plasma concentration of theophylline increased by **pentoxifylline**

Roflumilast: avoidance of theophylline advised by manufacturer of **roflumilast**

Sulfinpyrazone: plasma concentration of theophylline reduced by **sulfinpyrazone**

Sympathomimetics: manufacturer of theophylline advises avoid concomitant use with **ephedrine** in children

Sympathomimetics, Beta₂: increased risk of hypokalaemia when theophylline given with high doses of **beta₂ sympathomimetics**—*see* Hypokalaemia, p. 136

- Ulcer-healing Drugs: metabolism of theophylline inhibited by **cimetidine** (increased plasma concentration); absorption of theophylline possibly reduced by **sucralfate** (give at least 2 hours apart)

Theophylline (*continued*)

Vaccines: plasma concentration of theophylline possibly increased by **influenza vaccine**

Thiazolidinediones *see* Antidiabetics**Thiopental** *see* Anaesthetics, General**Thiotepa**

- Antipsychotics: avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)
- Muscle Relaxants: thiotepa enhances effects of **suxamethonium**

Thioxanthenes *see* Antipsychotics**Thyroid Hormones**

Anticids: absorption of levothyroxine possibly reduced by **antacids**

Anti-arrhythmics: for concomitant use of thyroid hormones and **amiodarone** *see* p. 82

Antibacterials: metabolism of levothyroxine accelerated by **rifampicin** (may increase requirements for levothyroxine in hypothyroidism)

- Anticoagulants: thyroid hormones enhance anticoagulant effect of **●coumarins** and **●phenindione**
- Antidepressants: thyroid hormones enhance effects of **amitriptyline** and **imipramine**; thyroid hormones possibly enhance effects of **tricyclics**

Antiepileptics: metabolism of thyroid hormones accelerated by **carbamazepine** and **phenobarbital** (may increase requirements for thyroid hormones in hypothyroidism); metabolism of thyroid hormones accelerated by **phenytoin** (may increase requirements in hypothyroidism), also plasma concentration of phenytoin possibly increased

Beta-blockers: levothyroxine accelerates metabolism of **propranolol**

Calcium Salts: absorption of levothyroxine reduced by **calcium salts**

Colestilan: manufacturer of colestilan advises give levothyroxine at least 1 hour before or 3 hours after **colestilan**

Cytotoxics: plasma concentration of levothyroxine possibly reduced by **imatinib**

Iron: absorption of levothyroxine reduced by **oral iron** (give at least 2 hours apart)

Lanthanum: absorption of levothyroxine reduced by **lanthanum** (give at least 2 hours apart)

Lipid-regulating Drugs: absorption of levothyroxine reduced by **colestevam**; absorption of thyroid hormones reduced by **colestipol** and **colestyramine**

Oestrogens: requirements for thyroid hormones in hypothyroidism may be increased by **oestrogens**

Orlistat: possible increased risk of hypothyroidism when levothyroxine given with **orlistat**

Polystyrene Sulfonate Resins: absorption of levothyroxine reduced by **polystyrene sulfonate resins**

Sevelamer: absorption of levothyroxine possibly reduced by **sevelamer**

Ulcer-healing Drugs: absorption of levothyroxine reduced by **cimetidine** and **sucralfate**

Tiagabine

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **●tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **●SSRIs** and **●tricyclics** (convulsive threshold lowered)

Antiepileptics: plasma concentration of tiagabine reduced by **carbamazepine**, **phenobarbital** and **phenytoin**

- Antimalarials: anticonvulsant effect of antiepileptics antagonised by **●mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **●antipsychotics** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with **●orlistat**

Tiaprofenic Acid *see* NSAIDs**Tibolone**

Antibacterials: metabolism of tibolone accelerated by **rifampicin** (reduced plasma concentration)

Antiepileptics: metabolism of tibolone accelerated by **carbamazepine** (reduced plasma concentration); metabolism of tibolone accelerated by **phenytoin**

Ticagrelor

- Antibacterials: plasma concentration of ticagrelor possibly increased by **●clarithromycin**—manufacturer of ticagrelor advises avoid concomitant use; plasma concentration of ticagrelor possibly increased by **erythromycin**; plasma concentration of ticagrelor reduced by **●rifampicin**

- Anticoagulants: ticagrelor increases plasma concentration of **●dabigatran**

Antidepressants: possible increased risk of bleeding when ticagrelor given with **●citalopram**, **●paroxetine** or **●sertraline**

Antiepileptics: plasma concentration of ticagrelor possibly reduced by **carbamazepine**, **phenobarbital** and **phenytoin**

- Antivirals: plasma concentration of ticagrelor possibly increased by **●atazanavir** and **●ritonavir**—manufacturer of ticagrelor advises avoid concomitant use
- Calcium-channel Blockers: plasma concentration of ticagrelor increased by **diltiazem**

- Cardiac Glycosides: ticagrelor increases plasma concentration of **●digoxin**

Ciclosporin: plasma concentration of ticagrelor increased by **ciclosporin**

Corticosteroids: plasma concentration of ticagrelor possibly reduced by **dexamethasone**

- Ergot Alkaloids: ticagrelor possibly increases plasma concentration of **●ergot alkaloids**

- Lipid-regulating Drugs: ticagrelor increases plasma concentration of **●simvastatin** (increased risk of toxicity)

Ticarcillin *see* Penicillins**Tigecycline**

Anticoagulants: tigecycline possibly enhances anticoagulant effect of **coumarins**

Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Timolol *see* Beta-blockers**Tinidazole**

Alcohol: possibility of disulfiram-like reaction when tinidazole given with **alcohol**

Antibacterials: plasma concentration of tinidazole possibly reduced by **rifampicin**

Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Tinzaparin *see* Heparins**Tioguanine**

- Antipsychotics: avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)
- Cytotoxics: increased risk of hepatotoxicity when tioguanine given with **busulfan**

Tiotropium *see* Antimuscarinics**Tipranavir**

Analgesics: plasma concentration of tipranavir possibly reduced by **buprenorphine**

Antacids: absorption of tipranavir reduced by **antacids**

- Antibacterials: tipranavir increases plasma concentration of **●clarithromycin** (reduce dose of clarithromycin in renal impairment), also plasma concentration of tipranavir increased by clarithromycin; tipranavir increases plasma concentration of **●rifabutin** (reduce dose of rifabutin); plasma concentration of tipranavir possibly reduced by **●rifampicin**—avoid concomitant use; avoidance of concomitant tipranavir in severe renal and hepatic impairment advised by manufacturer of **●telithromycin**

Anticoagulants: avoidance of tipranavir advised by manufacturer of **apixaban** and **rivaroxaban**

Tipranavir (*continued*)

- Antidepressants: plasma concentration of tipranavir possibly reduced by ●**St John's wort**—avoid concomitant use
- Antiepileptics: plasma concentration of tipranavir possibly reduced by ●**carbamazepine**
- Antifungals: plasma concentration of tipranavir increased by ●**fluconazole**
- Antimalarials: caution with tipranavir advised by manufacturer of ●**artemether with lumefantrine**; tipranavir possibly increases plasma concentration of ●**quinine** (increased risk of toxicity)
- Antimuscarinics: avoidance of tipranavir advised by manufacturer of ●**darifenacin**
- Antipsychotics: tipranavir possibly increases plasma concentration of ●**aripiprazole** (reduce dose of aripiprazole—consult aripiprazole product literature); tipranavir possibly increases plasma concentration of ●**quetiapine**—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: tipranavir reduces plasma concentration of ●**abacavir**, ●**fosamprenavir**, ●**lopinavir**, ●**saquinavir** and ●**zidovudine**; plasma concentration of tipranavir increased by ●**atazanavir** (also plasma concentration of atazanavir reduced); tipranavir reduces plasma concentration of ●**didanosine**—manufacturer of tipranavir advises tipranavir and didanosine capsules should be taken at least 2 hours apart; tipranavir reduces the plasma concentration of ●**dolutegravir** (see Dose under Dolutegravir, p. 324); tipranavir reduces plasma concentration of ●**etravirine**, also plasma concentration of tipranavir increased (avoid concomitant use)
- Beta-blockers: manufacturer of tipranavir advises avoid concomitant use with ●**metoprolol** for heart failure
- Bosentan: manufacturer of tipranavir advises avoid concomitant use with ●**bosentan**
- Lipid-regulating Drugs: increased risk of myopathy when tipranavir given with ●**atorvastatin** (see Dose under Atorvastatin, p. 125); tipranavir possibly increases plasma concentration of ●**rosuvastatin**—manufacturer of rosuvastatin advises avoid concomitant use; tipranavir possibly increases plasma concentration of ●**simvastatin**—avoid concomitant use; avoidance of tipranavir advised by manufacturer of ●**lomitapide** (plasma concentration of lomitapide possibly increased)
- Orlistat: absorption of tipranavir possibly reduced by ●**orlistat**
- Ranolazine: tipranavir possibly increases plasma concentration of ●**ranolazine**—manufacturer of ranolazine advises avoid concomitant use
- Sympathomimetics, Beta-1: manufacturer of tipranavir advises avoid concomitant use with ●**salmeterol**
- Ulcer-healing Drugs: tipranavir reduces plasma concentration of ●**esomeprazole** and ●**omeprazole**
- Vardenafil: manufacturer of tipranavir advises caution with ●**varidenafil**
- Vitamins: increased risk of bleeding when tipranavir given with high doses of ●**vitamin E**

Tirofiban

- Iloprost: increased risk of bleeding when tirofiban given with ●**iloprost**

Tizanidine *see* Muscle Relaxants**Tobramycin** *see* Aminoglycosides**Tocilizumab**

- Vaccines: avoid concomitant use of tocilizumab with live ●**vaccines** (see p. 604)

Tolazoline *see* Alpha-blockers**Tolbutamide** *see* Antidiabetics**Tolcapone**

- Antidepressants: avoid concomitant use of tolcapone with ●**MAOIs**
- Mementine: effects of dopaminergics possibly enhanced by ●**mementine**

Tolcapone (*continued*)

Methyl dopa: antiparkinsonian effect of dopaminergics antagonised by ●**methyl dopa**

Tolfenamic Acid *see* NSAIDs**Tolterodine** *see* Antimuscarinics**Tolvaptan**

Antibacterials: plasma concentration of tolvaptan reduced by ●**rifampicin**

Cardiac Glycosides: tolvaptan increases plasma concentration of ●**digoxin** (increased risk of toxicity)

- Grapefruit juice: plasma concentration of tolvaptan increased by ●**grapefruit juice**—avoid concomitant use

Topiramate

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by ●**MAOIs** and ●**tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by ●**SSRIs** and ●**tricyclics** (convulsive threshold lowered)
 - Antidiabetics: topiramate possibly increases plasma concentration of ●**metformin**; topiramate possibly reduces plasma concentration of ●**glibenclamide**
 - Antiepileptics: plasma concentration of topiramate often reduced by ●**carbamazepine**; topiramate reduces plasma concentration of ●**perampanel**; plasma concentration of topiramate possibly reduced by ●**phenobarbital**; topiramate increases plasma concentration of ●**phenytoin** (also plasma concentration of topiramate reduced); hyperammonaemia and CNS toxicity reported when topiramate given with ●**valproate**
 - Antimalarials: anticonvulsant effect of antiepileptics antagonised by ●**mefloquine**
 - Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ●**antipsychotics** (convulsive threshold lowered)
 - Diuretics: plasma concentration of topiramate possibly increased by ●**hydrochlorothiazide**
 - Lithium: topiramate possibly affects plasma concentration of ●**lithium**
 - Oestrogens: topiramate accelerates metabolism of ●**oestrogens** (reduced contraceptive effect—see p. 402)
 - Orlistat: possible increased risk of convulsions when antiepileptics given with ●**orlistat**
 - Progestogens: topiramate accelerates metabolism of ●**progestogens** (reduced contraceptive effect—see p. 402)
- Torsemide** *see* Diuretics
- Toremifene**
- Anticoagulants: toremifene possibly enhances anticoagulant effect of ●**coumarins**
 - Antiepileptics: metabolism of toremifene possibly accelerated by ●**carbamazepine** (reduced plasma concentration); metabolism of toremifene accelerated by ●**phenobarbital** (reduced plasma concentration); metabolism of toremifene possibly accelerated by ●**phenytoin**
 - Cytotoxics: possible increased risk of ventricular arrhythmias when toremifene given with ● **vandetanib**—avoid concomitant use
 - Diuretics: increased risk of hypercalcaemia when toremifene given with ●**thiazides and related diuretics**
- Trabectedin**
- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)
- Tramadol** *see* Opioid Analgesics
- Trandolapril** *see* ACE Inhibitors
- Tranylcypromine** *see* MAOIs
- Trastuzumab**
- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)
- Trazodone** *see* Antidepressants, Tricyclic (related)
- Tretinoin** *see* Retinoids

Triamcinolone *see* Corticosteroids

Triamterene *see* Diuretics

Trientine

Iron: trientine reduces absorption of **oral iron**

Zinc: trientine reduces absorption of **zinc**, also absorption of trientine reduced by zinc

Trifluoperazine *see* Antipsychotics

Trihexyphenidyl *see* Antimuscarinics

Trimethoprim

ACE Inhibitors: possible increased risk of hyperkalaemia when trimethoprim given with **ACE inhibitors**

Angiotensin-II Receptor Antagonists: possible increased risk of hyperkalaemia when trimethoprim given with **angiotensin-II receptor antagonists**

Anti-arrhythmics: possible increased risk of ventricular arrhythmias when trimethoprim (as co-trimoxazole) given with **amiodarone**—manufacturer of amiodarone advises avoid concomitant use of co-trimoxazole

Antibacterials: plasma concentration of trimethoprim possibly reduced by **rifampicin**; plasma concentration of both drugs may increase when trimethoprim given with **dapsone**

Anticoagulants: trimethoprim possibly enhances anticoagulant effect of **coumarins**

Antidiabetics: trimethoprim possibly enhances hypoglycaemic effect of **repaglinide**—manufacturer advises avoid concomitant use; trimethoprim rarely enhances the effects of **sulfonylureas**

- Antiepileptics: trimethoprim increases plasma concentration of **phenytoin** (also increased antifolate effect)

- Antimalarials: increased antifolate effect when trimethoprim given with **pyrimethamine**

Antivirals: trimethoprim (as co-trimoxazole) increases plasma concentration of **lamivudine**—avoid concomitant use of high-dose co-trimoxazole

- Azathioprine: increased risk of haematological toxicity when trimethoprim (also with co-trimoxazole) given with **azathioprine**

Cardiac Glycosides: trimethoprim possibly increases plasma concentration of **digoxin**

- Ciclosporin: increased risk of nephrotoxicity when trimethoprim given with **ciclosporin**, also plasma concentration of ciclosporin reduced by *intravenous* trimethoprim

- Cytotoxics: increased risk of haematological toxicity when trimethoprim (also with co-trimoxazole) given with **mercaptopurine** or **methotrexate**

Diuretics: increased risk of hyperkalaemia when trimethoprim given with **eplerenone**; possible increased risk of hyperkalaemia when trimethoprim given with **spironolactone**

Vaccines: antibacterials inactivate **oral typhoid vaccine**—*see* p. 626

Trimipramine *see* Antidepressants, Tricyclic

Tripotassium Dicitratobismuthate

Antibacterials: tripotassium dictratobismuthate reduces absorption of **tetracyclines**

Tropicamide *see* Antimuscarinics

Tropium *see* Antimuscarinics

Typhoid Vaccine (oral) *see* Vaccines

Typhoid Vaccine (parenteral) *see* Vaccines

Ubidecarenone

Anticoagulants: ubidecarenone may enhance or reduce anticoagulant effect of **warfarin**

Ulcer-healing Drugs *see* Histamine H₂-antagonists, Proton Pump Inhibitors, Sucralfate, and Tripotassium Dicitratobismuthate

Ulipristal

- Antacids: manufacturer of *high-dose* ulipristal advises avoid concomitant use with **antacids** (contraceptive effect of ulipristal possibly reduced)

Ulipristal (*continued*)

- Antibacterials: manufacturer of ulipristal advises avoid concomitant use with **clarithromycin** and **telithromycin**; plasma concentration of ulipristal increased by **erythromycin**—manufacturer of ulipristal advises avoid concomitant use; manufacturer of ulipristal advises avoid concomitant use with **rifampicin** (contraceptive effect of ulipristal possibly reduced)

Anticoagulants: manufacturer of ulipristal advises give **dabigatran** at least 1.5 hours before or after ulipristal

- Antidepressants: manufacturer of ulipristal advises avoid concomitant use with **St John's wort** (contraceptive effect of ulipristal possibly reduced)

- Antiepileptics: manufacturer of ulipristal advises avoid concomitant use with **carbamazepine**, **phenobarbital** and **phenytoin** (contraceptive effect of ulipristal possibly reduced)

Antifungals: manufacturer of ulipristal advises avoid concomitant use with **itraconazole**

Antihistamines: manufacturer of ulipristal advises give **fexofenadine** at least 1.5 hours before or after ulipristal

- Antivirals: manufacturer of ulipristal advises avoid concomitant use with **ritonavir** (contraceptive effect of ulipristal possibly reduced)

Calcium-channel Blockers: manufacturer of ulipristal advises avoid concomitant use with **verapamil**

Cardiac Glycosides: manufacturer of ulipristal advises give **digoxin** at least 1.5 hours before or after ulipristal

Grapefruit Juice: manufacturer of ulipristal advises avoid concomitant use with **grapefruit juice**

- Progestogens: ulipristal possibly reduces contraceptive effect of **progestogens**

- Ulcer-healing Drugs: manufacturer of *high-dose* ulipristal advises avoid concomitant use with **histamine H₂-antagonists** and **proton pump inhibitors** (contraceptive effect of ulipristal possibly reduced)

Ursodeoxycholic Acid *see* Bile Acids

Ustekinumab

- Vaccines: avoid concomitant use of ustekinumab with live **vaccines** (*see* p. 604)

Vaccines

Note For a general warning on live vaccines and high doses of corticosteroids or other immunosuppressive drugs, *see* p. 604; for advice on live vaccines and immunoglobulins, *see* under Normal Immunoglobulin, p. 628

- Abatacept: avoid concomitant use of live vaccines with **abatacept** (*see* p. 604)
- Adalimumab: avoid concomitant use of live vaccines with **adalimumab** (*see* p. 604)
- Anakinra: avoid concomitant use of live vaccines with **anakinra** (*see* p. 604)
- Antibacterials: oral typhoid vaccine inactivated by **antibacterials**—*see* p. 626
- Anticoagulants: influenza vaccine possibly enhances anticoagulant effect of **warfarin**
- Antiepileptics: influenza vaccine enhances effects of **phenytoin**
- Antimalarials: oral typhoid vaccine inactivated by **antimalarials**—*see* p. 626
- Belimumab: avoid concomitant use of live vaccines with **belimumab** (*see* p. 604)
- Certolizumab pegol: avoid concomitant use of live vaccines with **certolizumab pegol** (*see* p. 604)
- Corticosteroids: immune response to vaccines impaired by high doses of **corticosteroids**, avoid concomitant use with live vaccines (*see* p. 604)
- Cytotoxics: avoid concomitant use of live vaccines with **pixantrone** (*see* p. 604)
- Etanercept: avoid concomitant use of live vaccines with **etanercept** (*see* p. 604)
- Golimumab: avoid concomitant use of live vaccines with **golimumab** (*see* p. 604)

Vaccines (continued)

- **Infliximab**: avoid concomitant use of live vaccines with **●infliximab** (see p. 604)
- Interferons: avoidance of vaccines advised by manufacturer of **interferon gamma**
- **Leflunomide**: avoid concomitant use of live vaccines with **●leflunomide** (see p. 604)
- **Teriflunomide**: avoid concomitant use of live vaccines with **●teriflunomide** (see p. 604)
- Theophylline**: influenza vaccine possibly increases plasma concentration of **theophylline**
- **Tocilizumab**: avoid concomitant use of live vaccines with **●tocilizumab** (see p. 604)
- **Ustekinumab**: avoid concomitant use of live vaccines with **●ustekinumab** (see p. 604)

Valaciclovir *see* Aciclovir

Valganciclovir *see* Ganciclovir

Valproate

Analgesics: effects of valproate enhanced by **aspirin**

- **Antibacterials**: metabolism of valproate possibly inhibited by **erythromycin** (increased plasma concentration); avoidance of valproate advised by manufacturer of **●pivmecillinam**; plasma concentration of valproate reduced by **●carbapenems**—avoid concomitant use
- Anticoagulants**: valproate possibly enhances anticoagulant effect of **coumarins**
- **Antidepressants**: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **●tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **●SSRIs** and **●tricyclics** (convulsive threshold lowered)
- **Antiepileptics**: plasma concentration of valproate reduced by **carbamazepine**, also plasma concentration of active metabolite of carbamazepine increased; valproate possibly increases plasma concentration of **ethosuximide**; valproate increases plasma concentration of **●lamotrigine** (increased risk of toxicity—reduce lamotrigine dose); valproate sometimes reduces plasma concentration of an active metabolite of **oxcarbazepine**; valproate increases plasma concentration of **phenobarbital** (also plasma concentration of valproate reduced); valproate increases or possibly decreases plasma concentration of **phenytoin**, also plasma concentration of valproate reduced; valproate possibly increases plasma concentration of **rufinamide** (reduce dose of rufinamide); hyperammonaemia and CNS toxicity reported when valproate given with **topiramate**
- **Antimalarials**: anticonvulsant effect of antiepileptics antagonised by **●mefloquine**
- **Antipsychotics**: anticonvulsant effect of antiepileptics antagonised by **●antipsychotics** (convulsive threshold lowered); valproate possibly increases or decreases plasma concentration of **clozapine**; increased risk of side-effects including neutropenia when valproate given with **●olanzapine**
- Antivirals**: plasma concentration of valproate possibly reduced by **ritonavir**; valproate possibly increases plasma concentration of **zidovudine** (increased risk of toxicity)
- Anxiolytics and Hypnotics**: plasma concentration of valproate possibly increased by **clobazam**; increased risk of side-effects when valproate given with **clonazepam**; valproate possibly increases plasma concentration of **diazepam** and **lorazepam**
- Bupropion**: valproate inhibits the metabolism of **bupropion**
- Cytotoxics**: valproate increases plasma concentration of **temozolomide**
- Lipid-regulating Drugs**: absorption of valproate possibly reduced by **colestyramine**
- Oestrogens**: plasma concentration of valproate possibly reduced by **ethinylestradiol**

Valproate (continued)

- **Orlistat**: possible increased risk of convulsions when antiepileptics given with **●orlistat**
- Sodium Benzoate**: valproate possibly reduces effects of **sodium benzoate**
- Sodium Phenylbutyrate**: valproate possibly reduces effects of **sodium phenylbutyrate**
- **Ulcer-healing Drugs**: metabolism of valproate inhibited by **●cimetidine** (increased plasma concentration)

Valsartan *see* Angiotensin-II Receptor Antagonists

Vancomycin

Anaesthetics, General: hypersensitivity-like reactions can occur when *intravenous* vancomycin given with **general anaesthetics**

- **Antibacterials**: increased risk of nephrotoxicity and ototoxicity when vancomycin given with **●aminoglycosides**, **capreomycin** or **colistimethate sodium**; increased risk of nephrotoxicity when vancomycin given with **polymyxins**
- Antifungals**: possible increased risk of nephrotoxicity when vancomycin given with **amphotericin**
- **Ciclosporin**: increased risk of nephrotoxicity when vancomycin given with **●ciclosporin**
- Cytotoxics**: increased risk of nephrotoxicity and possibly of ototoxicity when vancomycin given with **cisplatin**
- **Diuretics**: increased risk of ototoxicity when vancomycin given with **●loop diuretics**
- Lipid-regulating Drugs**: effects of *oral* vancomycin antagonised by **colestyramine**
- **Muscle Relaxants**: vancomycin enhances effects of **●suxamethonium**
- Tacrolimus**: possible increased risk of nephrotoxicity when vancomycin given with **●tacrolimus**
- Vaccines**: antibacterials inactivate **oral typhoid vaccine**—see p. 626

Vandetanib

- **Analgesics**: possible increased risk of ventricular arrhythmias when vandetanib given with **●methadone**—avoid concomitant use
- **Anti-arrhythmics**: possible increased risk of ventricular arrhythmias when vandetanib given with **●amiodarone** or **●disopyramide**—avoid concomitant use
- **Antibacterials**: possible increased risk of ventricular arrhythmias when vandetanib given with **parenteral ●erythromycin**—avoid concomitant use; possible increased risk of ventricular arrhythmias when vandetanib given with **●moxifloxacin**—avoid concomitant use; plasma concentration of vandetanib reduced by **●rifampicin**—manufacturer of vandetanib advises avoid concomitant use
- Antidepressants**: manufacturer of vandetanib advises avoid concomitant use with **St John's wort** (plasma concentration of vandetanib possibly reduced)
- Antidiabetics**: vandetanib possibly increases plasma concentration of **metformin** (consider reducing dose of metformin)
- Antiepileptics**: manufacturer of vandetanib advises avoid concomitant use with **carbamazepine** and **phenobarbital** (plasma concentration of vandetanib possibly reduced)
- **Antihistamines**: possible increased risk of ventricular arrhythmias when vandetanib given with **●mizolastine**—avoid concomitant use
- **Antimalarials**: possible increased risk of ventricular arrhythmias when vandetanib given with **●artemether with lumefantrine**—avoid concomitant use
- **Antipsychotics**: possible increased risk of ventricular arrhythmias when vandetanib given with **●amisulpride**, **●chlorpromazine**, **●haloperidol**, **●pimozide**, **●sulpride** or **●zuclopenthixol**—avoid concomitant use; avoid concomitant use of cytotoxics with **●clozapine** (increased risk of agranulocytosis)

Vandetanib (*continued*)

- Beta-blockers: possible increased risk of ventricular arrhythmias when vandetanib given with **•sotalol**—avoid concomitant use
- Cardiac Glycosides: vandetanib increases plasma concentration of **digoxin**—possible increased risk of bradycardia
- Cytotoxics: possible increased risk of ventricular arrhythmias when vandetanib given with **•arsenic trioxide**—avoid concomitant use
- Hormone Antagonists: possible increased risk of ventricular arrhythmias when vandetanib given with **•toremifene**—avoid concomitant use
- 5HT₂-receptor Antagonists: increased risk of ventricular arrhythmias when vandetanib given with **•ondansetron**—avoid concomitant use
- Pentamidine Isetionate: possible increased risk of ventricular arrhythmias when vandetanib given with **•pentamidine isetionate**—avoid concomitant use

Vardenafil

- Alpha-blockers: enhanced hypotensive effect when vardenafil given with **•alpha-blockers**—separate doses by 6 hours (except with tamsulosin)—see also under Phosphodiesterase type-5 inhibitors, BNF section 7.4.5
- Anti-arrhythmics: avoidance of vardenafil advised by manufacturer of **disopyramide** (risk of ventricular arrhythmias)
- Antibacterials: plasma concentration of vardenafil possibly increased by **clarithromycin** (consider reducing initial dose of vardenafil); plasma concentration of vardenafil increased by **erythromycin** (reduce dose of vardenafil)
- Antifungals: plasma concentration of vardenafil possibly increased by **•itraconazole**—avoid concomitant use
- Antivirals: plasma concentration of vardenafil possibly increased by **fosamprenavir**; plasma concentration of vardenafil increased by **•indinavir** and **•ritonavir**—avoid concomitant use; increased risk of ventricular arrhythmias when vardenafil given with **•saquinavir**—avoid concomitant use; avoidance of vardenafil advised by manufacturer of **•telaprevir**; caution with vardenafil advised by manufacturer of **tipranavir**
- Calcium-channel Blockers: enhanced hypotensive effect when vardenafil given with **nifedipine**
- Cobicistat: plasma concentration of vardenafil possibly increased by **•cobicistat**—manufacturer of cobicistat advises reduce dose of vardenafil (consult cobicistat product literature)
- Dapoxetine: avoidance of vardenafil advised by manufacturer of **dapoxetine**
- Grapefruit Juice: plasma concentration of vardenafil possibly increased by **•grapefruit juice**—avoid concomitant use
- Nicorandil: possible increased hypotensive effect when vardenafil given with **•nicorandil**—avoid concomitant use
- Nitrates: possible increased hypotensive effect when vardenafil given with **•nitrates**—avoid concomitant use

Varicella-zoster Vaccine *see* Vaccines

Vasodilator Antihypertensives

- ACE Inhibitors: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **ACE inhibitors**
- Adrenergic Neurone Blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **adrenergic neurone blockers**
- Alcohol: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **alcohol**
- Aldesleukin: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **aldesleukin**

Vasodilator Antihypertensives (*continued*)

- Alpha-blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **alpha-blockers**
- Anaesthetics, General: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **general anaesthetics**
- Analgesics: hypotensive effect of hydralazine, minoxidil and sodium nitroprusside antagonised by **NSAIDs**
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **angiotensin-II receptor antagonists**
- Antidepressants: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **MAOIs**; enhanced hypotensive effect when hydralazine or sodium nitroprusside given with **tricyclic-related antidepressants**
- Antipsychotics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **phenothiazines**
- Anxiolytics and Hypnotics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **anxiolytics and hypnotics**
- Beta-blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **beta-blockers**
- Calcium-channel Blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **calcium-channel blockers**
- Clonidine: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **clonidine**
- Corticosteroids: hypotensive effect of hydralazine, minoxidil and sodium nitroprusside antagonised by **corticosteroids**
- Diazoxide: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **diazoxide**
- Diuretics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **diuretics**
- Dopaminergics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **levodopa**
- Methyldopa: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **methyldopa**
- Moxisylyte: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **moxisylyte**
- Moxonidine: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **moxonidine**
- Muscle Relaxants: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **baclofen**; enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **tizanidine**
- Nicorandil: possible enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **nicorandil**
- Nitrates: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **nitrates**
- Oestrogens: hypotensive effect of hydralazine, minoxidil and sodium nitroprusside antagonised by **oestrogens**
- Prostaglandins: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with **alprostadil**
- Vasodilator Antihypertensives: enhanced hypotensive effect when hydralazine given with **minoxidil** or **sodium nitroprusside**; enhanced hypotensive effect when minoxidil given with **sodium nitroprusside**

Vecuronium *see* Muscle Relaxants**Vemurafenib**

Antibacterials: manufacturer of vemurafenib advises avoid concomitant use with **rifabutin** and **rifampicin**

- Anticoagulants: vemurafenib possibly enhances anticoagulant effect of **warfarin**

Antidepressants: manufacturer of vemurafenib advises avoid concomitant use with **St John's wort**

Antiepileptics: manufacturer of vemurafenib advises avoid concomitant use with **carbamazepine** and **phenytoin**

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Cytotoxics: avoidance of vemurafenib advised by manufacturer of **ipilimumab**
- Oestrogens: manufacturer of vemurafenib advises contraceptive effect of **oestrogens** possibly reduced
- Progestogens: manufacturer of vemurafenib advises contraceptive effect of **progestogens** possibly reduced

Venlafaxine

- Analgesics: increased risk of bleeding when venlafaxine given with **NSAIDs** or **aspirin**; possible increased serotonergic effects when SSRI-related antidepressants given with **fentanyl**; possible increased serotonergic effects when venlafaxine given with **tramadol**

- Anticoagulants: venlafaxine possibly enhances anticoagulant effect of **warfarin**; possible increased risk of bleeding when SSRI-related antidepressants given with **dabigatran**

- Antidepressants: possible increased serotonergic effects when venlafaxine given with **St John's wort**, **duloxetine** or **mirtazapine**; enhanced CNS effects and toxicity when venlafaxine given with **MAOIs** (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping venlafaxine); after stopping SSRI-related antidepressants do not start **moclobemide** for at least 1 week

- Antimalarials: avoidance of antidepressants advised by manufacturer of **artemether with lumefantrine** and **piperaquine with arteminol**

Antipsychotics: venlafaxine increases plasma concentration of **haloperidol**

Atomoxetine: possible increased risk of convulsions when antidepressants given with **atomoxetine**

- Dapoxetine: possible increased risk of serotonergic effects when venlafaxine given with **dapoxetine** (manufacturer of dapoxetine advises venlafaxine should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping venlafaxine)

- Dopaminergics: caution with venlafaxine advised by manufacturer of **entacapone**; increased risk of hypertension and CNS excitation when venlafaxine given with **selegiline** (selegiline should not be started until 1 week after stopping venlafaxine, avoid venlafaxine for 2 weeks after stopping selegiline)

5HT₁-receptor Agonists: possible increased serotonergic effects when venlafaxine given with **5HT₁ agonists**

Lithium: possible increased serotonergic effects when venlafaxine given with **lithium**

- Methylthionium: risk of CNS toxicity when SSRI-related antidepressants given with **methylthionium**—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthionium and observe patient for up to 4 hours after administration)

Verapamil *see* Calcium-channel Blockers**Vigabatrin**

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **tricyclics**

Vigabatrin

- Antidepressants (*continued*)

related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIs** and **tricyclics** (convulsive threshold lowered)

Antiepileptics: vigabatrin reduces plasma concentration of **phenytoin**

- Antimalarials: anticonvulsant effect of antiepileptics antagonised by **mefloquine**
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by **antipsychotics** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with **orlistat**

Vilanterol *see* Sympathomimetics, Beta₂**Vildagliptin** *see* Antidiabetics**Vinblastine**

- Aldesleukin: avoidance of vinblastine advised by manufacturer of **aldesleukin**

- Antibacterials: toxicity of vinblastine increased by **erythromycin**—avoid concomitant use

- Antifungals: possible increased risk of vinblastine toxicity when given with **itraconazole**; metabolism of vinblastine possibly inhibited by **posaconazole** (increased risk of neurotoxicity)

- Antimalarials: avoidance of vinblastine advised by manufacturer of **piperaquine with arteminol**

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Antivirals: plasma concentration of vinblastine possibly increased by **ritonavir**

Vincristine

- Antifungals: increased risk of vincristine toxicity when given with **itraconazole**; metabolism of vincristine possibly inhibited by **posaconazole** (increased risk of neurotoxicity)

- Antimalarials: avoidance of vincristine advised by manufacturer of **piperaquine with arteminol**

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Calcium-channel Blockers: metabolism of vincristine possibly inhibited by **nifedipine**

Cardiac Glycosides: vincristine possibly reduces absorption of **digoxin tablets**

Vindesine

- Antifungals: possible increased risk of vindesine toxicity when given with **itraconazole**

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

Vinflunine

- Antibacterials: plasma concentration of vinflunine possibly reduced by **rifampicin**—manufacturer of vinflunine advises avoid concomitant use

- Antidepressants: plasma concentration of vinflunine possibly reduced by **St John's wort**—manufacturer of vinflunine advises avoid concomitant use

- Antifungals: possible increased risk of vinflunine toxicity when given with **itraconazole**

- Antimalarials: avoidance of vinflunine advised by manufacturer of **piperaquine with arteminol**

- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

- Antivirals: plasma concentration of vinflunine possibly increased by **ritonavir**—manufacturer of vinflunine advises avoid concomitant use

Grapefruit Juice: plasma concentration of vinflunine possibly increased by **grapefruit juice**—manufacturer of vinflunine advises avoid concomitant use

Vinorelbine

- Antibacterials: possible increased risk of neutropenia when vinorelbine given with **clarithromycin**

- Antifungals: possible increased risk of vinorelbine toxicity when given with **itraconazole**

Vinorelbine (*continued*)

- Antimalarials: avoidance of vinorelbine advised by manufacturer of ●**piperaquine with arteminol**
- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)

Vismodegib

- Antibacterials: manufacturer of vismodegib advises avoid concomitant use with ●**rifampicin** (plasma concentration of vismodegib possibly reduced)
- Antidepressants: manufacturer of vismodegib advises avoid concomitant use with ●**St John's wort** (plasma concentration of vismodegib possibly reduced)
- Antiepileptics: manufacturer of vismodegib advises avoid concomitant use with ●**carbamazepine** and ●**phenytoin** (plasma concentration of vismodegib possibly reduced)
- Antipsychotics: avoid concomitant use of cytotoxics with ●**clozapine** (increased risk of agranulocytosis)

Vitamin A *see* Vitamins

Vitamin D *see* Vitamins

Vitamin E *see* Vitamins

Vitamin K (Phytomenadione) *see* Vitamins

Vitamins

- Antibacterials: absorption of vitamin A possibly reduced by ●**neomycin**
- Anticoagulants: vitamin E possibly enhances anticoagulant effect of ●**coumarins**; vitamin K antagonises anticoagulant effect of ●**coumarins** and ●**phenindione**
- Antiepileptics: vitamin D requirements possibly increased when given with ●**carbamazepine**, ●**phenobarbital** or ●**phenytoin**
- Antivirals: increased risk of bleeding when high doses of vitamin E given with ●**tipranavir**
- Ciclosporin: vitamin E possibly affects plasma concentration of ●**ciclosporin**
- Diuretics: increased risk of hypercalcaemia when vitamin D given with ●**thiazides and related diuretics**
- Dopaminergics: pyridoxine reduces effects of ●**levodopa** when given without dopa-decarboxylase inhibitor
- Lipid-regulating Drugs: absorption of calcitriol possibly reduced by ●**colestyramine** (give at least 1 hour before or 4 to 6 hours after colestyramine)
- Retinoids: risk of hypervitaminosis A when vitamin A given with ●**retinoids**—avoid concomitant use
- Selenium: ascorbic acid possibly reduces absorption of ●**selenium** (give at least 4 hours apart)
- Sevelamer: absorption of calcitriol reduced by ●**sevelamer** (give at least 1 hour before or 3 hours after sevelamer)

Voriconazole *see* Antifungals, Triazole

Warfarin *see* Coumarins

Xipamide *see* Diuretics

Xylometazoline *see* Sympathomimetics

Zafirlukast *see* Leukotriene Receptor Antagonists

Zaleplon *see* Anxiolytics and Hypnotics

Zidovudine

Note Increased risk of toxicity with nephrotoxic and myelosuppressive drugs—for further details consult product literature

Analgesics: increased risk of haematological toxicity when zidovudine given with ●**NSAIDs**; plasma concentration of zidovudine possibly increased by ●**methadone**

Antibacterials: absorption of zidovudine reduced by ●**clarithromycin** tablets (give at least 2 hours apart); manufacturer of zidovudine advises avoid concomitant use with ●**rifampicin**

Zidovudine (*continued*)

Antiepileptics: zidovudine increases or decreases plasma concentration of ●**phenytoin**; plasma concentration of zidovudine possibly increased by ●**valproate** (increased risk of toxicity)

- Antifungals: plasma concentration of zidovudine increased by ●**fluconazole** (increased risk of toxicity)

Antimalarials: increased antifolate effect when zidovudine given with ●**pyrimethamine**

- Antivirals: profound myelosuppression when zidovudine given with ●**ganciclovir** (if possible avoid concomitant administration, particularly during initial ganciclovir therapy); increased risk of granulocytopenia when zidovudine given with ●**nevirapine**; increased risk of anaemia when zidovudine given with ●**ribavirin**—avoid concomitant use; zidovudine possibly inhibits effects of ●**stavudine** (manufacturers advise avoid concomitant use); plasma concentration of zidovudine reduced by ●**tipranavir**

Atovaquone: plasma concentration of zidovudine increased by ●**atovaquone** (increased risk of toxicity)

- Orlistat: absorption of zidovudine possibly reduced by ●**orlistat**
- Probenecid: excretion of zidovudine reduced by ●**probenecid** (increased plasma concentration and risk of toxicity)

Zinc

Antibacterials: zinc reduces absorption of ●**ciprofloxacin**, ●**levofloxacin**, ●**moxifloxacin** and ●**ofloxacin**; zinc reduces absorption of ●**norfloxacin** (give at least 2 hours apart); zinc reduces absorption of ●**tetracyclines**, also absorption of zinc reduced by tetracyclines

Calcium Salts: absorption of zinc reduced by ●**calcium salts**

Eltrombopag: zinc possibly reduces absorption of ●**eltrombopag** (give at least 4 hours apart)

Iron: absorption of zinc reduced by ●**oral iron**, also absorption of ●**oral iron** reduced by zinc

Penicillamine: absorption of zinc reduced by ●**penicillamine**, also absorption of penicillamine reduced by zinc

Trientine: absorption of zinc reduced by ●**trientine**, also absorption of trientine reduced by zinc

Zoledronic Acid *see* Bisphosphonates

Zolmitriptan *see* 5HT₁-receptor Agonists (under HT)

Zolpidem *see* Anxiolytics and Hypnotics

Zonisamide

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by ●**MAOIs** and ●**tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by ●**SSRIs** and ●**tricyclics** (convulsive threshold lowered)

Antiepileptics: plasma concentration of zonisamide reduced by ●**carbamazepine**, ●**phenobarbital** and ●**phenytoin**

- Antimalarials: anticonvulsant effect of antiepileptics antagonised by ●**mefloquine**

- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ●**antipsychotics** (convulsive threshold lowered)

Diuretics: manufacturer of zonisamide advises avoid concomitant use with ●**carbonic anhydrase inhibitors** in children

- Orlistat: possible increased risk of convulsions when antiepileptics given with ●**orlistat**

Zopiclone *see* Anxiolytics and Hypnotics

Zuclopenthixol *see* Antipsychotics

A2 Borderline substances

A2.1	Enteral feeds (non-disease specific)	772
A2.1.1	Enteral feeds (non-disease specific): less than 5 g protein/100 mL	772
A2.1.2	Enteral feeds (non-disease specific): 5 g (or more) protein/100 mL	774
A2.1.3	Enteral feeds (non-disease specific): Child under 12 years	778
A2.2	Nutritional supplements (non-disease specific)	783
A2.2.1	Nutritional supplements: less than 5 g protein/100 mL	783
A2.2.2	Nutritional supplements: 5 g (or more) protein/100 mL	785
A2.3	Specialised formulas	791
A2.3.1	Specialised formulas: Infant and child	791
A2.3.2	Specialised formulas for specific clinical conditions	800
A2.4	Feed supplements	801
A2.4.1	High-energy supplements	801
A2.4.2	Fibre, vitamin, and mineral supplements	806
A2.5	Feed additives	807
A2.5.1	Special additives for conditions of intolerance	807
A2.5.2	Feed thickeners and pre-thickened drinks	807
A2.5.3	Flavouring preparations	807
A2.6	Foods for special diets	808
A2.6.1	Gluten-free foods	808
A2.6.2	Low-protein foods	810
A2.7	Nutritional supplements for metabolic diseases	811

In certain conditions some foods (and toilet preparations) have characteristics of drugs and the Advisory Committee on Borderline Substances (ACBS) advises as to the circumstances in which such substances may be regarded as drugs. Prescriptions issued in accordance with the Committee's advice and endorsed 'ACBS' will normally not be investigated.

General Practitioners are reminded that the ACBS recommends products on the basis that they may be regarded as drugs for the management of specified conditions. Doctors should satisfy themselves that the products can safely be prescribed, that patients are adequately monitored and that, where necessary, expert hospital supervision is available.

Foods which may be prescribed on FP10, GP10 (Scotland), or WP10 (Wales) All the food products listed in this appendix have ACBS approval. The clinical condition for which the product has been approved is included with each entry.

Note Foods included in this appendix may contain cariogenic sugars and appropriate oral hygiene measures should be taken.

Enteral feeds and nutritional supplements For most enteral feeds and nutritional supplements, the main source of **carbohydrate** is either maltodextrin or glucose syrup; other carbohydrate sources are listed in the relevant table, below. Feeds containing residual lactose (less than 1 g lactose/100 mL formula) are described as 'clinically lactose-free' or 'lactose-free' by some manufacturers. The presence of lactose (including residual lactose) in feeds is indicated in the relevant table, below. The primary sources of **protein** or **amino acids** are included with each product entry. The **fat** or **oil** content is derived from a variety of sources such as vegetables, soya bean, corn, palm nuts, and seeds; where the fat content is derived from animal or fish sources, this information is included in the relevant table, below. The presence of medium chain triglycerides (MCT) is also noted where the quantity exceeds 30% of the fat content.

Enteral feeds and nutritional supplements can contain varying amounts of **vitamins**, **minerals**, and **trace elements**—the manufacturer's product literature should be consulted for more detailed information. For further information on enteral nutrition, see section 9.4.2. Feeds containing vitamin K may affect the INR in children receiving warfarin; see **interactions**: Appendix 1 (vitamins).

The suitability of food products for patients requiring a vegan, kosher, halal, or other compliant diet should be confirmed with individual manufacturers.

Note Feeds containing more than 6 g/100 mL protein or 2 g/100 mL fibre should be avoided in children unless recommended by an appropriate specialist or dietician.

Standard ACBS indications:

Disease-related malnutrition, intractable malabsorption, pre-operative preparation of malnourished patients, dysphagia, proven inflammatory bowel disease, following total gastrectomy, short-bowel syndrome, bowel fistula

Paediatric ACBS indications:

Disease-related malnutrition, intractable malabsorption, growth failure, pre-operative preparation of malnourished patients, dysphagia, short-bowel syndrome, bowel fistula

Prices quoted in Appendix 2 are basic NHS net prices; for further information see Prices in BNFC.

A2.1 Enteral feeds (non-disease specific)

A2.1.1 Enteral feeds (non-disease specific): less than 5 g protein/100 mL

A2.1.1.1 Enteral feeds: 1 kcal/mL and less than 5 g protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Fresubin® Original (Fresenius Kabi)	Liquid (sip or tube feed) per 100 mL	420 kJ (100 kcal)	3.8 g cows' milk soya	13.8 g (sugars 3.5 g ¹)	3.4 g	Nil	Gluten-free Residual lactose Contains fish gelatin Feed in flexible pack contains fish oil and fish gelatin	Standard, p. 771	Bottle: 200 mL = £2.07 Black currant, chocolate, nut, peach, vanilla Flexible pack: 500 mL = £4.02 1000 mL = £7.96 1500 mL = £11.95
Fresubin® Original Fibre (Fresenius Kabi)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	3.8 g cows' milk soya	13 g (sugars 0.9 g)	3.4 g	1.5 g	Gluten-free Residual lactose Contains fish oil	Standard, p. 771 except bowel fistula and pre-operative preparation of malnourished patients. Not suitable for child under 2 years	Flexible pack: 500 mL = £4.55 1000 mL = £9.08
Fresubin® 1500 Complete (Fresenius Kabi)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	3.8 g cows' milk soya	13 g (sugars 0.9 g)	3.4 g	1.5 g	Gluten-free Residual lactose Contains fish oil	Standard, p. 771 except bowel fistula and pre-operative preparation of malnourished patients. Not suitable for child under 2 years	Flexible pack: 1500 mL = £12.81
Jevity® (Abbott)	Liquid (tube feed) per 100 mL	449 kJ (107 kcal)	4 g caseinates	14.1 g (sugars 470 mg)	3.47 g	1.76 g	Gluten-free Residual lactose	Standard, p. 771 except bowel fistula. Not suitable for child under 2 years	Flexible pack: 500 mL = £4.80 1000 mL = £9.02 1500 mL = £13.55
Novasource® GI Control (Nestlé)	Liquid (tube feed) per 100 mL	444 kJ (106 kcal)	4.1 g cows' milk	14.4 g (sugars 500 mg)	3.5 g (MCT 40 %)	2.2 g	Gluten-free Residual lactose	Standard, p. 771	Flexible pack: 500 mL = £4.78
Nutrison® (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	4 g cows' milk	12.3 g (sugars 1 g)	3.9 g	Nil	Gluten-free Residual lactose	Standard, p. 771	Bottle: 500 mL = £4.23 Flexible pack: 500 mL = £4.70 1000 mL = £8.25 1500 mL = £12.35

1. Sugar content varies with flavour

Nutrison® Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	4 g cows' milk	12.3 g (sugars 1 g)	3.9 g	1.5 g	Gluten-free Residual lactose	Standard, p. 771 except bowel fistula	Bottle: 500 mL = £4.77 Flexible pack: 500 mL = £5.08 1000 mL = £9.54 1500 mL = £14.31
Osmolite® (Abbott)	Liquid (tube feed) per 100 mL	424 kJ (100 kcal)	4 g caseinates soy isolate	13.6 g (sugars 630 mg)	3.4 g	Nil	Gluten-free Residual lactose	Standard, p. 771	Can: 250 mL = £2.17 Bottle: 500 mL = £4.12 1000 mL = £7.76 1500 mL = £11.63
Soya protein formula (see also section A2.3.1)									
Fresubin® Soya Fibre (Fresenius Kabi)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	3.8 g soya protein	13.3 g (sugars 4.1 g)	3.6 g	2 g	Gluten-free Lactose-free Contains fish oil	Standard, p. 771; <i>also</i> cows' milk protein intolerance, lactose intolerance	Flexible pack: 500 mL = £4.71
Nutrison® Soya (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	4 g soy isolate	12.3 g (sugars 1 g)	3.9 g	Nil	Gluten-free Residual lactose Milk protein-free	Standard, p. 771; <i>also</i> cows' milk protein and lactose intolerance	Bottle: 500 mL = £5.07 Flexible pack: 1000 mL = £10.15
Nutrison® Soya Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	4 g soy isolate	12.3 g (sugars 700 mg)	3.9 g	1.5 g	Gluten-free Residual lactose Milk protein-free	Standard, p. 771 except bowel fistula; <i>also</i> cows' milk protein and lactose intolerance	Flexible pack: 1500 mL = £16.88
Peptide-based formula									
Peptamen® (Nestlé)	Liquid (sip or tube feed) per 100 mL	420 kJ (100 kcal)	4 g whey peptides	12.7 g (sugars 480 mg ¹)	3.7 g (MCT 70 %)	Nil	Gluten-free Residual lactose	Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula	Bottle: 200 mL = £2.83 Vanilla Flexible pack: 500 mL = £6.66 1000 mL = £12.50
Peptisorb® (Nutricia Clinical)	Liquid (tube feed) per 100 mL	425 kJ (100 kcal)	4 g whey protein hydrolysate	17.6 g (sugars 1.7 g)	1.7 g (MCT 47 %)	Nil	Gluten-free Residual lactose	Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula	Bottle: 500 mL = £6.73 Flexible pack: 500 mL = £7.38 1000 mL = £13.32
Survimed® OPD (Fresenius Kabi)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	4.5 g whey protein hydrolysate	14.3 g (sugars 1.1 g)	2.8 g (MCT 51 %)	100 mg	Gluten-free Residual lactose Contains fish oil	Standard, p. 771; <i>also</i> growth failure	Flexible pack: 500 mL = £6.71 1000 mL = £13.42
1. Sugar content varies with flavour									

A2.1.1.2 Enteral feeds: Less than 1 kcal/mL and less than 5 g protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Amino acid formula (essential and non-essential amino acids)									
Elemental 028® Extra (Nutricia Clinical)	Liquid (sip feed) per 100 mL	360 kJ (86 kcal)	2.5 g (protein equivalent)	11 g (sugars 4.7 g)	3.5 g (MCT 35 %)	Nil		Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula	Carton: 250 mL = £3.50 Grapefruit, orange and pineapple, summer fruits
	Standard dilution (20 %) of powder (sip or tube feed) per 100 mL	374 kJ (89 kcal) ¹	2.5 g (protein equivalent)	11.8 g (sugars 1.8 g)	3.5 g (MCT 35 %)	Nil			Sachet: 100 g = £6.81 Banana, citrus, orange, unflavoured ²
Powder provides protein equivalent 12.5 g, carbohydrate 59 g, fat 17.45 g, energy 1871 kJ (443 kcal)/100 g									
1. Nutritional values vary with flavour—consult product literature									
2. Flavouring: see <i>Modjul</i> ® Flavour System, p. 807									

A2.1.2 Enteral feeds (non-disease specific): 5 g (or more) protein/100 mL**A2.1.2.1 Enteral feeds: 1.5 kcal/mL and 5 g (or more) protein/100 mL**

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Fresubin® 2250 Complete (Fresenius Kabi)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	5.6 g cows' milk	18.8 g (sugars 1.5 g)	5.8 g	2 g	Gluten-free Residual lactose Contains fish oil and fish gelatin	Standard, p. 771	Flexible pack: 1500 mL = £14.29
Fresubin® Energy (Fresenius Kabi)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	5.6 g cows' milk	18.8 g (sugars ¹)	5.8 g	Nil	Gluten-free ² Residual lactose Contains fish gelatin	Standard, p. 771	Bottle: 200 mL = £1.97 Banana, black currant, cappuccino, chocolate, l emon, neutral, strawberry, tropical fruits, vanilla
	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	5.6 g cows' milk	18.8 g (sugars 1.4 g)	5.8 g	Nil	Gluten-free Residual lactose Contains fish oil and fish gelatin	Standard, p. 771	Flexible pack: 500 mL = £4.92 1000 mL = £9.67 1500 mL = £12.96
1. Sugar content varies with flavour									
2. Strawberry flavour may contain traces of wheat starch and egg									

Fresubin® Energy Fibre (Fresenius Kabi)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	5.6 g cows' milk	18.8 g (sugars ¹)	5.8 g	2 g	Gluten-free Residual lactose Contains fish gelatin	Standard, p. 771	Bottle: 200 mL = £1.98 Banana, caramel, cherry, chocolate, strawberry, vanilla
	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	5.6 g cows' milk	18.8 g (sugars 1.5 g)	5.8 g	2 g	Gluten-free Residual lactose Contains fish oil and fish gelatin	Standard, p. 771	Flexible pack: 500 mL = £5.40 1000 mL = £10.29
Fresubin® HP Energy (Fresenius Kabi)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	7.5 g cows' milk	17 g (sugars 1 g)	5.8 g (MCT 57%)	Nil	Gluten-free Residual lactose Contains fish oil and fish gelatin	Standard, p. 771; <i>also</i> CAPD and haemodialysis	Flexible pack: 500 mL = £5.01 1000 mL = £10.03
Jevity® 1.5 kcal (Abbott)	Liquid (tube feed) per 100 mL	649 kJ (154 kcal)	6.38 g caseinates and soy isolate	20.1 g (sugars 1.47 g)	4.9 g	2.2 g	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 2 years; not recommended for child 2–10 years	Flexible pack: 500 mL = £5.68 1000 mL = £10.86 1500 mL = £16.63
Novasource® GI Forte (Nestlé)	Liquid (tube feed) per 100 mL	631 kJ (150 kcal)	6 g cows' milk	18.3 g (sugars 1.8 g)	5.9 g	2.2 g	Gluten-free Residual lactose	Standard, p. 771	Flexible pack: 500 mL = £5.39 1000 mL = £10.44
Nutrison® Energy (Nutricia Clinical)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	6 g cows' milk	18.5 g (sugars 1.5 g)	5.8 g	Nil	Gluten-free Residual lactose	Standard, p. 771	Bottle: 500 mL = £5.12 Flexible pack: 500 mL = £5.47 1000 mL = £10.29 1500 mL = £15.39
Nutrison® Energy Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	6 g cows' milk	18.5 g (sugars 1.5 g)	5.8 g	1.5 g	Gluten-free Residual lactose	Standard, p. 771	Bottle: 500 mL = £5.72 Flexible pack: 500 mL = £6.07 1000 mL = £11.42 1500 mL = £17.63
1. Sugar content varies with flavour									

A2.1.2.1 Enteral feeds: 1.5 kcal/mL and 5 g (or more) protein/100 mL (*product list continued*)

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Osmolite® 1.5 kcal (Abbott)	Liquid (tube feed) per 100 mL	632 kJ (150 kcal)	6.25 g cows' milk soya protein isolate	20 g (sugars 4.9 g)	5 g	Nil	Gluten-free Residual lactose	Standard, p. 771	Flexible pack: 500 mL = £5.05 1000 mL = £9.68 1500 mL = £14.49
Resource® Energy (Nestlé)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	5.6 g cows' milk	21 g (sugars 5.2 g ¹)	5 g	less than 500 mg	Gluten-free Residual lactose	Standard, p. 771 Not suitable for use in child under 3 years	Bottle: 4 × 200 mL = £7.67 Apricot, banana, chocolate, coffee, strawberry-raspberry, vanilla
1. Sugar content varies with flavour									

A2.1.2.2 Enteral feeds: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Fresubin® 1000 Complete (Fresenius Kabi)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	5.5 g cows' milk	12.5 g (sugars 1.1 g)	3.1 g	2 g	Gluten-free Residual lactose Contains fish oil	Standard, p. 771	Flexible pack: 1000 mL = £10.29
Fresubin® 1200 Complete (Fresenius Kabi)	Liquid (tube feed) per 100 mL	500 kJ (120 kcal)	6 g cows' milk	15 g (sugars 1.22 g)	4.1 g	2 g	Gluten-free Residual lactose Contains fish oil	Standard, p. 771	Flexible pack: 1000 mL = £13.11
Fresubin® 1800 Complete (Fresenius Kabi)	Liquid (tube feed) per 100 mL	500 kJ (120 kcal)	6 g cows' milk	15 g (sugars 1.22 g)	4.1 g	2 g	Gluten-free Residual lactose Contains fish oil	Standard, p. 771	Flexible pack: 1500 mL = £13.11
Jevity® Plus (Abbott)	Liquid (tube feed) per 100 mL	514 kJ (122 kcal)	5.5 g caseinates soy isolates	15.1 g (sugars 890 mg)	3.93 g	2.2 g	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 2 years; not recommended for child 2–10 years	Flexible pack: 500 mL = £5.24 1000 mL = £10.58 1500 mL = £15.88
Jevity® Plus HP (Abbott)	Liquid (tube feed) per 100 mL	551 kJ (131 kcal)	8.13 g cows' milk soy isolates	14.2 g (sugars 950 mg)	4.33 g	1.5 g	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis Not suitable for child under 2 years; not recommended for child 2–10 years	Flexible pack: 500 mL = £5.28
Jevity® Promote (Abbott)	Liquid (tube feed) per 100 mL	434 kJ (103 kcal)	5.55 g caseinates soy isolates	12 g (sugars 670 mg)	3.32 g	1.7 g	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 2 years; not recommended for child 2–10 years	Flexible pack: 1000 mL = £10.34

Nutrison® MCT (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	5 g cows' milk	12.6 g (sugars 1 g)	3.3 g (MCT 61%)	Nil	Gluten-free Residual lactose	Standard, p. 771	Flexible pack: 1000 mL = £9.53
Nutrison® Protein Plus (Nutricia Clinical)	Liquid (tube feed) per 100 mL	525 kJ (125 kcal)	6.3 g cows' milk	14.2 g (sugars 1.1 g)	4.9 g	Nil	Gluten-free Residual lactose	Standard, p. 771	Flexible pack: 1000 mL = £9.80
Nutrison® Protein Plus Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	525 kJ (125 kcal)	6.3 g cow's milk	14.1 g (sugars 1.1 g)	4.9 g	1.5 g	Gluten-free Residual lactose	Disease related malnutrition	Flexible pack: 1000 mL = £10.91
Nutrison® 800 Complete Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	345 kJ (83 kcal)	5.5 g cows' milk pea protein soya protein	8.8 g (sugars 600 mg)	2.5 g	1.5 g	Gluten-free Residual lactose Contains fish oil	Standard, p. 771 except bowel fistula Not suitable for child under 6 years; not recommended for child 6–12 years	Flexible pack: 1000 mL = £9.99
Nutrison® 1000 Complete Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	5.5 g cows' milk	11.3 g (sugars 700 mg)	3.7 g	2 g	Gluten-free Residual lactose	Disease related malnutrition in patients with low energy and/or low fluid requirements	Flexible pack: 1000 mL = £10.58
Nutrison® 1200 Complete Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	505 kJ (120 kcal)	5.5 g cows' milk	15 g (sugars 1.2 g)	4.3 g	2 g	Gluten-free Residual lactose	Standard, p. 771 except bowel fistula	Flexible pack: 1000 mL = £11.21 1500 mL = £16.83
Osmolite® Plus (Abbott)	Liquid (tube feed) per 100 mL	508 kJ (121 kcal)	5.55 g caseinates	15.8 g (sugars 730 mg)	3.93 g	Nil	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 10 years	Flexible pack: 500 mL = £4.83 1000 mL = £9.31 1500 mL = £13.94
Peptamen® HN (Nestlé)	Liquid (tube feed) per 100 mL	556 kJ (133 kcal)	6.6 g whey protein hydrolysates	15.6 g (sugars 1.4 g)	4.9 g (MCT 70%)	Nil	Gluten-free Residual lactose Hydrolysed with pork trypsin	Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula Not suitable for child under 3 years	Flexible pack: 500 mL = £7.17
Perative® (Abbott)	Liquid (sip or tube feed) per 100 mL	552 kJ (131 kcal)	6.7 g caseinate whey protein hydrolysates	17.7 g (sugars 660 mg)	3.7 g (MCT 42%)	Nil	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 5 years	Flexible pack: 500 mL = £6.73 1000 mL = £13.45

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Ensure® Twocal (Abbott)	Liquid (sip or tube feed) per 100 mL	838 kJ (200 kcal)	8.4 g cows' milk	21 g (sugars 4.5 g)	8.9 g	1 g	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> haemodialysis and CAPD	Bottle: 200 mL = £2.22 Banana, neutral, strawberry, vanilla

A2.1.3.1 Enteral feeds, Child: Less than 1 kcal/mL and less than 4 g protein/100 mL

[illegible]

SMA® High Energy (SMA Nutrition)	Liquid (sip feed) per 100 mL	382 kJ (91 kcal)	2 g whey protein and casein	9.8 g lactose	4.9 g	Nil	Contains lactose	Disease related malnutrition and malabsorption, and growth failure in child from birth to 18 months	Carton: 250 mL = £2.29
Amino acid formula (essential and non-essential amino acids)									
Emsogen® (SHS)	Standard dilution (20%) of powder (sip or tube feed) per 100 mL	368 kJ (88 kcal) ¹	2.5 g protein equivalent (essential and non- essential amino acids)	12 g (sugars 1.6 g)	3.3 g ² (MCT 83%)	Nil	Lactose-free	Short-bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula Not suitable for child under 1 year or as sole source of nutrition in child 1–5 years	Sachet: 100 g = £7.01 Orange, unflavoured ³
Powder provides: protein equivalent 12.5 g, carbohydrate 60 g, fat 16.4 g, energy 1839 kJ (438 kcal)/100 g									
1. Nutritional values vary with flavour—consult product literature 2. Additional source of alpha linolenic acid needed if used as sole source of nutrition 3. Flavouring: see <i>Modjul</i> ® Flavour System, p. 807									

A2.1.3.2 Enteral feeds, Child: 1 kcal/mL and less than 4 g protein/100 mL									
Not suitable for use in child under 1 year unless otherwise stated									
Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Fortini® 1.0 Multi Fibre (Nutricia Clinical)	Liquid (sip feed) per 100 mL	420 kJ (100 kcal) ¹	2.4 g cows' milk	11.8 g (sugars 4.7 g)	4.5 g	1.5 g	Gluten-free Residual lactose	Disease-related malnutrition and growth failure in child 1–6 years, body-weight 8–20 kg	Bottle: 200 mL = £2.41 Banana, chocolate, strawberry, vanilla
Frebini® Original (Fresenius Kabi)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	2.5 g cows' milk	12.5 g (sugars 700 mg)	4.4 g	Nil	Gluten-free Residual lactose Contains fish oils and fish gelatin	Standard, p. 771, and growth failure in child 1–10 years, body-weight 8–30 kg	Flexible pack: 500 mL = £5.94
Frebini® Original Fibre (Fresenius Kabi)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	2.5 g cows' milk	12.5 g (sugars 700 mg)	4.4 g	750 mg	Gluten-free Residual lactose Contains fish oils and fish gelatin	Standard, p. 771, and growth failure in child 1–10 years, body-weight 8–30 kg	Flexible pack: 500 mL = £6.61
Infatrin® (Nutricia Clinical)	Liquid (sip or tube feed) per 100 mL	415 kJ (100 kcal)	2.6 g cows' milk	10.3 g (lactose 5.2 g)	5.4 g	800 mg	Gluten-free Contains fish oil	Failure to thrive, disease-related malnutrition and malabsorption, in child from birth up to body-weight 8 kg	Bottle: 100 mL = £1.12 200 mL = £2.17 Flexible pack: 500 mL = £5.89

A2.1.3.2 Enteral feeds: Child: 1 kcal/mL and less than 4 g protein/100 mL (*product list continued*)

Not suitable for use in child under 1 year unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Nutrini® (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	2.8 g cows' milk	12.3 g (sugars 1 g)	4.4 g	Nil	Gluten-free Residual lactose	Standard, p. 771, and growth failure in child 1–6 years, body-weight 8–20 kg	Bottle: 200 mL = £2.63 Flexible pack: 500 mL = £6.53
Nutrini® Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	2.8 g whey protein and caseinate	12.3 g (sugars 800 mg)	4.4 g	800 mg	Gluten-free Residual lactose Contains fish oil	Standard, p. 771, and growth failure in child 1–6 years, body-weight 8–20 kg	Bottle: 200 mL = £2.91 Flexible pack: 500 mL = £7.25
Paediasure® (Abbott)	Liquid (sip or tube feed) per 100 mL	422 kJ (100 kcal) ¹	2.8 g cows' milk	11.2 g (sugars 3.92 g)	4.98 g	Nil	Gluten-free Residual lactose	Paediatric, p. 771 in child 1–10 years, body-weight 8–30 kg	Bottle: 200 mL = £2.37 Banana, chocolate, strawberry, vanilla Flexible pack: 500 mL = £6.05 Vanilla
Paediasure® Fibre (Abbott)	Liquid (sip or tube feed) per 100 mL	424 kJ (101 kcal) ¹	2.8 g caseinates and whey protein	10.9 g (sugars 3.84 g)	4.98 g	730 mg	Gluten-free Residual lactose	Paediatric, p. 771 in child 1–10 years, body-weight 8–30 kg	Bottle: 200 mL = £2.60 Banana, strawberry, vanilla Flexible pack: 500 mL = £6.73 Vanilla
Paediasure® Peptide (Abbott)	Liquid (sip or tube feed) per 100 mL	420 kJ (100 kcal)	3 g whey protein and caseinate	13 g (sugars 2.98 g)	4 g (MCT 50%)	Nil	Gluten-free Residual lactose	Standard, p. 771, and growth failure in child 1–10 years, body-weight 8–30 kg	Bottle: 200 mL = £3.82 Vanilla Flexible pack: 500 mL = £9.59 Vanilla
Similac® High Energy (Abbott)	Liquid (sip or tube feed) per 100 mL	419 kJ (100 kcal) ²	2.6 g cows' milk and whey protein	10.1 g (sugars 5.6 g)	5.2 g	400 mg	Gluten-free Contains lactose and soy oil	Increased energy requirements, faltering growth, and/or need for fluid restriction, in child body-weight up to 8 kg	Bottle: 60 mL = £0.65 200 mL = £2.10
Tentrini® (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	3.3 g whey protein and caseinate	12.3 g (sugars 800 mg)	4.2 g	Nil	Gluten-free Residual lactose Contains fish oil	Standard, p. 771, and growth failure in child 7–12 years, body-weight 21–45 kg	Flexible pack: 500 mL = £5.75
Tentrini® Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	3.3 g whey protein and caseinate	12.3 g (sugars 800 mg)	4.2 g	1.1 g	Gluten-free Residual lactose Contains fish oil	Standard, p. 771, except bowel fistula, and growth failure in child 7–12 years body-weight 21–45 kg	Flexible pack: 500 mL = £7.82

1. Nutritional values vary with flavour—consult product literature

2. Nutritional values vary with pack size—consult product literature

Hydrolysate Formula See also Infant Formula (Hydrolysate), section 2.3.1

Nutrini® Peptisorb (Nutricia Clinical)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	2.8 g whey protein hydrolysate	13.7 g (sugars 800 mg)	3.9 g (MCT 46 %)	Nil	Gluten-free Residual lactose	Standard, p. 771, and growth failure in child 1–6 years, body- weight 8–20 kg	Flexible pack: 500 mL = £10.18
Peptamen® Junior (Nestlé)	Liquid (tube feed) per 100 mL	420 kJ (100 kcal)	3 g whey protein hydrolysate	13.2 g	4 g (MCT 60 %)	Nil	Gluten-free Residual lactose Hydrolysed with pork trypsin	Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula, in child 1–10 years	Flexible pack: 500 mL = £6.65
	Standard dilution (22%) of powder (sip or tube feed) per 100 mL	420 kJ (100 kcal)	3 g whey protein hydrolysate	13.8 g	3.85 g (MCT 60 %)	Nil	Gluten-free Residual lactose Hydrolysed with bacterial trypsin		Can: 400 g = £17.45 Vanilla (7.86-g measuring scoop provided)
Powder provides: protein 13.7 g, carbohydrate 62.9 g, fat 17.5 g, energy 1910 kJ (457 kcal)/100 g									

A2.1.3.3 Enteral feeds, Child: More than 1 kcal/mL and less than 4 g protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Fortini® (Nutricia Clinical)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	3.4 g cows' milk	18.8 g (sugars 7.4 g)	6.8 g	Nil	Gluten-free Residual lactose	Disease-related malnutrition and growth failure in child 1–6 years, body-weight 8–20 kg	Bottle: 200 mL = £3.12 Strawberry, vanilla
Fortini® Multifibre (Nutricia Clinical)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	3.4 g cows' milk	18.8 g (sugars 7.4 g)	6.8 g	1.5 g	Gluten-free Residual lactose	Disease-related malnutrition and growth failure in child 1–6 years, body-weight 8–20 kg	Bottle: 200 mL = £3.28 Banana, chocolate, strawberry, vanilla, and unflavoured
Fortini® Smoothie Multifibre (Nutricia Clinical)	Liquid (sip feed) per 100 mL	625 kJ (150 kcal)	3.4 g cows' milk	19 g (sugars 11.5 g)	6.4 g	1.4 g	Gluten-free Residual lactose	Disease-related malnutrition and growth failure in child 1–6 years, body-weight 8–20 kg	Bottle: 200 mL = £3.28 Berry fruit, summer fruit
Frebini® Energy Drink (Fresenius Kabi)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	3.8 g cows' milk	18.7 g (sugars 4.5 g)	6.7 g	Nil	Gluten-free Residual lactose	Disease-related malnutrition and growth failure in child 1–10 years, body-weight 8–30 kg	Bottle: 200 mL = £2.82 Banana, strawberry
Frebini® Energy (Fresenius Kabi)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	3.75 g cows' milk	18.75 g (sugars 830 mg)	6.7 g	Nil	Gluten-free Residual lactose Contains fish oil and fish gelatin	Standard, p. 771, and failure in child 1–10 years, body-weight 8– 30 kg	Flexible pack: 500 mL = £7.45

A2.1.3.3 Enteral feeds, Child: More than 1 kcal/mL and less than 4 g protein/100 mL (*product list continued*)

Not suitable for use in child under 1 year unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Frebini® Energy Fibre Drink (Fresenius Kabi)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	3.8 g cows' milk	18.75 g (sugars 4.5 g ¹)	6.7 g	1.1 g	Gluten-free Residual lactose	Disease-related malnutrition and growth failure in child 1–10 years, body-weight 8–30 kg	Bottle: 200 mL = £2.88 Chocolate, vanilla
Frebini® Energy Fibre (Fresenius Kabi)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	3.75 g cows' milk	18.75 g (sugars 830 mg)	6.7 g	1.13 g	Gluten-free Residual lactose Contains fish oils and fish gelatin	Standard, p. 771, and growth failure in child 1–10 years, body-weight 8–30 kg	Flexible pack: 500 mL = £7.97
Resource® Junior (Nestlé)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal) ²	3 g cows' milk	20.6 g (sugars 4.9 g)	6.2 g	Nil	Gluten-free Residual lactose	Standard, p. 771 in child 1–10 years	Bottle: 200 mL = £2.09 Chocolate, strawberry, vanilla
1. Sugar content varies with flavour 2. Nutritional values vary with flavour—consult product literature									

A2.1.3.4 Enteral feeds, Child: 1.5 kcal/mL and more than 4 g protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Nutrini® Energy (Nutricia Clinical)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	4.1 g caseinate whey protein	18.5 g (sugars 1.1 g)	6.7 g	Nil	Gluten-free Residual lactose Contains fish oil	Standard, p. 771, and growth failure in child 1–6 years, body-weight 8–20 kg	Bottle: 200 mL = £3.20 Flexible pack: 500 mL = £8.19
Nutrini® Energy Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	4.1 g caseinate whey protein	18.5 g (sugars 1.1 g)	6.7 g	800 mg	Gluten-free Residual lactose Contains fish oil	Paediatric, p. 771 except bowel fistula; <i>also</i> total gastrectomy, in child 1–6 years, body-weight 8–20 kg	Bottle: 200 mL = £3.38 Flexible pack: 500 mL = £8.45
Paediasure® Plus (Abbott)	Liquid (sip or tube feed) per 100 mL	632 kJ (151 kcal)	4.2 g caseinates whey protein	16.7 g ¹	7.47 g	Nil	Gluten-free Residual lactose	Paediatric, p. 771 in child 1–10 years, body-weight 8–30 kg	Bottle: 200 mL = £2.89 Banana, strawberry, vanilla, unflavoured Flexible pack: 500 mL = £7.59 Vanilla
1. Sugar content varies with presentation									

Paediasure® Plus Fibre (Abbott)	Liquid (sip or tube feed) per 100 mL	635 kJ (152 kcal) ¹	4.2 g caseinates whey protein	16.4 g (sugars 5.3 g ²)	7.47 g	1.1 g	Gluten-free Residual lactose	Paediatric, p. 771 in child 1–10 years, body-weight 8–30 kg	Bottle: 200 mL = £3.14 Banana, strawberry, vanilla Flexible pack: 500 mL = £8.08 Vanilla
Peptamen® Junior Advance (Nestlé)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	4.5 g whey protein	18 g (sugars 2.1 g)	6.6 g (MCT 61%)	540 mg	Gluten-free Residual lactose Hydrolysed with pork trypsin Contains fish oil	Intractable malabsorption, short-bowel syndrome, bowel fistula, and proven inflammatory bowel disease in child 1–10 years	Flexible pack: 500 mL = £7.59
Tentrini® Energy (Nutricia Clinical)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	4.9 g whey protein and caseinate	18.5 g (sugars 1.1 g)	6.3 g	Nil	Gluten-free Residual lactose Contains fish oil	Standard, p. 771, and growth failure, in child 7–12 years, body-weight 21–45 kg	Flexible pack: 500 mL = £7.10
Tentrini® Energy Multi Fibre (Nutricia Clinical)	Liquid (tube feed) per 100 mL	630 kJ (150 kcal)	4.9 g whey protein and caseinate	18.5 g (sugars 1.1 g)	6.3 g	1.1 g	Gluten-free Residual lactose Contains fish oil	Paediatric, p. 771, and proven inflammatory bowel disease, in child 7–12 years, body-weight 21–45 kg	Flexible pack: 500 mL = £7.82
1. Nutritional values vary with flavour—consult product literature 2. Sugar content varies with presentation									

A2.2 Nutritional supplements (non-disease specific)

A2.2.1 Nutritional supplements: less than 5 g protein/100 mL

A2.2.1.1 Nutritional supplements: 1 kcal/mL and less than 5 g protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Ensure® (Abbott)	Liquid (sip or tube feed) per 100 mL	423 kJ (100 kcal) ¹	4 g caseinates soy isolate	13.6 g (sugars 3.93 g)	3.36 g	Nil	Gluten-free Residual lactose	Standard, p. 771	Can: 250 mL = £2.26 Chocolate, coffee, vanilla
1. Nutritional values vary with flavour—consult product literature									

A2.2.1.2 Nutritional supplements: More than 1 kcal/mL and less than 5 g protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
AYMES® Shake (AYMES)	Standard dilution of powder (57 g in 200 mL water) (sip feed) per 100 mL	530.5 kJ (126 kcal) ¹	4.5 g cows' milk	17.5 g (sugars 8.4 g)	4.2 g	Nil	Gluten-free Contains lactose	Standard, p. 771. Use with caution in child 1–6 years	Sachets: 7 × 57 g = £5.46 Banana, chocolate, neutral, strawberry, vanilla Sample pack (mixed): 5 × 57 g = £4.78
Powder 57 g reconstituted with 200 mL whole milk provides: protein 15.8 g, carbohydrate 44.1 g, fat 16.4 g, energy 1625 kJ (388 kcal)									
Ensure® Plus Juice (Abbott)	Liquid (sip feed) per 100 mL	638 kJ (150 kcal)	4.8 g whey protein isolate	32.7 g (sugars 9.4 g ²)	Nil	Nil	Gluten-free Residual lactose Non-milk taste	Standard, p. 771	Bottle: 220 mL = £1.97 Apple, fruit punch, lemon-lime, orange, peach, strawberry
Fortijuce® (Nutricia Clinical)	Liquid (sip feed) per 100 mL	640 kJ (150 kcal)	4.0 g cows' milk	33.5 g (sugars 13.1 g ²)	Nil	Nil	Gluten-free Residual lactose Non-milk taste	Standard, p. 771 Not suitable for child under 3 years	Bottle: 200 mL = £2.02 Apple, black currant, forest fruits, lemon, orange, strawberry, tropical Starter pack (mixed) 4 × 200 mL = £8.08
Fresubin® Jucy Drink (Fresenius Kabi)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	4 g whey protein	33.5 g (sugars 8 g)	Nil	Nil	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis	Bottle: 4 × 200 mL = £7.52 Apple, black currant, cherry, orange, pineapple
Paediasure® Plus Juice (Abbott)	Liquid (sip feed) per 100 mL	638 kJ (150 kcal) ¹	4.2 g cows' milk	33.3 g (sugars 9.4 g)	Nil	Nil	Gluten-free Residual lactose Non-milk taste	Nutritional supplement in child 1–10 years, body-weight 8–30 kg with disease-related malnutrition and, or growth failure	Bottle: 200 mL = £3.03 Apple, very berry
ProvideExtra® Juice Drink (Fresenius Kabi)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	4.0 g pea and soya protein hydrolysates	33.5 g ²	Nil	Nil ³	Gluten-free Lactose-free Non-milk taste Sweet-flavoured products contain fish gelatin	Standard, p. 771	Bottle: 200 mL = £1.75 Apple, black currant, cherry, lemon-lime, orange-pineapple
Resource® Dessert Energy (Nestlé)	Semi-solid per 100 g	671 kJ (160 kcal)	4.8 g cows' milk	21.2 g (sugars 9.9 g ²)	6.2 g	Nil	Gluten-free Contains lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis	Cup: 125 g = £1.59 Caramel, chocolate, vanilla
Resource® Fruit (Nestlé)	Liquid (sip feed) per 100 mL	520 kJ (125 kcal)	4 g whey protein hydrolysate	27 g (sugars 9.5 g ²)	less than 200 mg	less than 200 mg ³	Gluten-free Residual lactose Non-milk taste	Standard, p. 771 Not suitable for child under 3 years	Bottle: 4 × 200 mL = £7.35 Apple, orange, pear-cherry, raspberry-black currant

1. Nutritional values vary with flavour—consult product literature
2. Sugar content varies with flavour
3. Fibre content varies with flavour

A2.2.2 Nutritional supplements: 5 g (or more) protein/100 mL

A2.2.2.1 Nutritional supplements: 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Ensure® Plus Fibre (Abbott)	Liquid (sip or tube feed) per 100 mL	652 kJ (155 kcal) ¹	6.25 g cows' milk soya protein isolate	20.2 g (sugars 5.5 g)	4.92 g	2.5 g	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis	Bottle: 200 mL = £2.02 Banana, chocolate, raspberry, strawberry, vanilla
Ensure® Plus Milkshake style (Abbott)	Liquid (sip or tube feed) per 100 mL	632 kJ (150 kcal) ¹	6.25 g cows' milk soya protein isolate	20.2 g (sugars 6.89 g)	4.92 g	Nil	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis	Bottle: 220 mL = £2.02 Banana, chocolate, coffee, fruits of the forest, orange, peach, raspberry, strawberry, vanilla, neutral
Ensure® Plus Savoury (Abbott)	Liquid (sip or tube feed) per 100 mL	632 kJ (150 kcal) ¹	6.25 g cows' milk soy protein isolate	20.2 g (sugars 1.13 g)	4.92 g	Nil	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis	Bottle: 220 mL = £2.02 Chicken, mushroom
Ensure® Plus Yoghurt style (Abbott)	Liquid (sip feed) per 100 mL	632 kJ (150 kcal) ¹	6.25 g cows' milk	20.2 g (sugars 11.7 g)	4.92 g	Nil	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis	Bottle: 220 mL = £2.02 Peach, strawberry
Ensure® Plus Commence (Abbott)	Starter pack (5–10 day's supply), contains: <i>Ensure® Plus Milkshake Style</i> (various flavours), 1 pack (10 × 220-mL) = £20.23.								
Fortisip® Bottle (Nutricia Clinical)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	6 g cows' milk	18.4 g ²	5.8 g	Nil	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 200 mL = £2.06 Banana, chocolate, neutral, orange, strawberry, toffee, tropical fruits, vanilla
Fortisip® Multi Fibre (Nutricia Clinical)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	6 g cows' milk	18.4 g (sugars 7.0 g)	5.8 g	2.3 g	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 200 mL = £2.09 Vanilla

1. Nutritional values vary with flavour—consult product literature

2. Sugar content varies with flavour

A2.2.2.1 Nutritional supplements: 1.5 kcal/mL and 5 g (or more) protein/100 mL (*product list continued*)

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Fortisip® Savoury Multi Fibre (Nutricia Clinical)	Liquid (sip feed) per 100 mL	625 kJ (150 kcal)	7.5 g cows' milk	12.8 g (sugars 900 mg)	7 g	2.3 g	Gluten-free Residual lactose	Standard, p. 771 except bowel fistula Not suitable for child under 3 years; use with caution in child 3–6 years	Bottle: 2 × 200 mL = £4.32 Chicken
Fortisip® Yoghurt Style (Nutricia Clinical)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	6 g cows' milk	18.7 g (sugars 10.8 g)	5.8 g	200 mg	Gluten-free Contains lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 200 mL = £2.02 Peach-orange, raspberry, vanilla-lemon
Fortisip® Range (Nutricia Clinical)	Starter pack contains 4 × Fortisip® Bottle, 4 × Fortijuice®, 2 × Fortisip® Yogurt Style, 1 pack (10 × 200 mL) = £20.20.								
Fresubin® Protein Energy Drink (Fresenius Kabi)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	10 g cows' milk	12.4 g (sugars 6.4 g ¹)	6.7 g	Nil ²	Gluten-free Residual lactose Contains fish gelatin	Standard, p. 771; also CAPD, haemodialysis	Bottle: 200 mL = £1.97 Cappuccino, chocolate, strawberry, tropical fruits, vanilla
Fresubin® Thickened (Fresenius Kabi)	Liquid (sip feed) per 100 mL	630 kJ (150 kcal)	10 g cows' milk	12.2 g (sugars 7.1 g ³)	6.7 g	480 mg ⁴	Gluten-free Residual lactose	Dysphagia or disease-related malnutrition Not suitable for child under 3 years.	Bottle: 200 mL = £2.10 Syrup (Stage 1) and custard (Stage 2) consistencies Strawberry, vanilla
Fresubin® YOcrème (Fresenius Kabi)	Semi-solid per 100 g	630 kJ (150 kcal)	7.5 g whey protein	19.5 g (sugars 16.8 g)	4.7 g	Nil	Gluten-free Contains lactose	Dysphagia, or presence or risk of malnutrition Not suitable for child under 3 years	Pot: 4 × 125 g = £7.72 Apricot-peach, biscuit, lemon, raspberry
Nutriplen® Protein (Nualtra)	Liquid (sip feed) per 100 mL	632 kJ (150 kcal)	10 g cows' milk soya protein	15 g (sugars 4.6 g)	5.6 g	Nil	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 3 years; use with caution in child 3–6 years	Bottle: 4 × 200 mL = £5.80 Strawberry, vanilla

1. Sugar content varies with flavour
2. Fibre content varies with flavour
3. Sugar content varies with consistency
4. Fibre content varies with consistency

A2.2.2.2 Nutritional supplements: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Clinutren® Dessert (Nestlé)	Semi-solid per 100 g	520 kJ (125 kcal)	9.5 g cows' milk	15.5 g (sugars 14 g ¹)	2.6 g	500 mg ²	Gluten-free Contains lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis Not suitable for child under 3 years	Pot: 4 × 125 g = £5.88 Caramel, chocolate, peach, vanilla
Ensure® Plus Crème (Abbott)	Semi-solid per 100 g	574 kJ (137 kcal) ³	5.68 g cow's milk soy protein isolates	18.4 g (sugars 12.4 g)	4.47 g	Nil	Gluten-free Residual lactose Contains soya	Standard, p. 771; <i>also</i> CAPD, haemodialysis Not suitable for child under 3 years	Pot: 125 g = £1.72 Banana, chocolate, neutral, vanilla
Fortimel® Regular (Nutricia Clinical)	Liquid (sip feed) per 100 mL	420 kJ (100 kcal)	10 g cows' milk	10.3 g (sugars 8.1 g ¹)	2.1 g	Nil	Gluten-free Contains lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 200 mL = £1.57 Chocolate, forest fruits, strawberry, vanilla
Nutrilis® Fruit Stage 3 (Nutricia Clinical)	Semi-Solid per 100 g	560 kJ (133 kcal)	7 g whey isolate	16.7 g (sugars 11.3 g)	4 g	2.6 g	Gluten-free Residual lactose	Standard, p. 771 except bowel fistula; <i>also</i> CAPD, haemodialysis Not suitable for child under 3 years	Pot: 3 × 150 g = £7.08 Apple, strawberry
Oral Impact® (Nestlé)	Standard dilution of powder (74 g in 250 mL water) (sip feed) per 100 mL	425 kJ (101 kcal) ³	5.6 g cows' milk	13.4 g (sugars 7.4 g)	2.8 g	1 g	Residual lactose Contains fish oil	Pre-operative nutritional supplement for malnourished patients or patients at risk of malnourishment Not suitable for child under 3 years	Sachet: 5 × 74 g = £16.93 Citrus, coffee, tropical
Powder provides: protein 16.8 g, carbohydrate 40.2 g, fat 8.3 g, fibre 3 g, energy 1276 kJ (303 kcal)/74 g									
Resource® Protein (Nestlé)	Liquid (sip feed) per 100 mL	530 kJ (125 kcal) ³	9.4 g cows' milk	14 g (sugars 4.5 g)	3.5 g	Nil	Gluten-free Contains lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 200 mL = £1.45 Apricot, chocolate, forest fruits, strawberry, vanilla
1. Sugar content varies with flavour 2. Fibre content varies with flavour 3. Nutritional values vary with flavour—consult product literature									

A2.2.2.3 Nutritional supplements: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Complan® Shake (Complan Foods)	Powder per 57 g	1057 kJ (251 kcal) ¹	8.8 g cows' milk	35.2 g (sugars 22.7 g)	8.4 g	Trace	Gluten-free Contains lactose	Standard, p. 771	Sachet: 4 × 57 g = £3.78 Banana, chocolate, original, strawberry, vanilla Starter pack: 5 × 57 g = £5.32
Powder 57 g reconstituted with 200 mL whole milk provides: protein 15.6 g, carbohydrate 44.5 g, fat 16.4 g, energy 1621 kJ (387 kcal)									
Foodlink® Complete (Foodlink)	Powder per 100 g	1838 kJ (437 kcal) ¹	21.9 g cows' milk	57.3 g	13.3 g	Nil	Contains lactose	Standard, p. 771	Carton: 450 g = £3.19 Banana, chocolate, neutral, strawberry
Recommended serving = 3 heaped tablespoonfuls in 250 mL water provides: protein 12.5 g, carbohydrate 32.7 g, fat 7.6 g, energy 1048 kJ (249 kcal) ¹									
Foodlink® Complete with Fibre (Foodlink)	Powder per 100 g	1804 kJ (428 kcal) ¹	19.5 g cows' milk	57.1 g (sugars 36.8 g)	12.3 g	8 g	Contains lactose	Standard, p. 771	Sachet: 10 × 63 g = £6.67 Vanilla + fibre
Recommended serving = 4 heaped tablespoonfuls in 250 mL water provides: protein 12.3 g, carbohydrate 38 g, fat 7.5 g, fibre 5 g, energy 1137 kJ (270 kcal) ¹									
Forticreme® Complete (Nutricia Clinical)	Semi-solid per 100 g	675 kJ (160 kcal)	9.5 g cows' milk	19.2 g (sugars 10.6 g)	5 g	100 mg ²	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis Not suitable for child under 3 years	Pot: 4 × 125 g = £7.84 Banana, chocolate, forest fruits, vanilla
Fortisip® Compact (Nutricia Clinical)	Liquid (sip feed) per 100 mL	1010 kJ (240 kcal)	9.6 g cows' milk	29.7 g (sugars 15 g)	9.3 g	Nil	Residual lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 125 mL = £1.85 Apricot, banana, chocolate, forest fruits, mocha, strawberry, vanilla Starter pack: 6 × 125 mL = £12.12
Fortisip® Compact Fibre(Nutricia Clinical)	Liquid (sip feed) per 100 mL	1000 kJ (240 kcal)	9.4 g cows' milk	25.2 g (sugars 13.9 g)	10.4 g	3.6 g	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 125 mL = £1.91 Mocha, strawberry, vanilla Starter pack: 4 × 125 mL = £8.36
Fortisip® Compact Protein (Nutricia Clinical)	Liquid (sip feed) per 100 mL	1010 kJ (240 kcal) ¹	14.4 g cows' milk	24.4 g (sugars 13.3 g)	9.4 g	Nil	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 4 × 125 mL = £7.76 Banana, mocha, strawberry, vanilla
Fortisip® Extra (Nutricia Clinical)	Liquid (sip feed) per 100 mL	675 kJ (160 kcal)	10 g cows' milk	18.1 g (sugars 9 g)	5.3 g	Nil ²	Gluten-free Contains lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 200 mL = £2.08 Chocolate, forest fruits, mocha, strawberry, vanilla Starter pack: forest fruits, 4 × 200 mL = £8.32

1. Nutritional values vary with flavour—consult product literature

2. Fibre content varies with flavour

Fresubin® 2 kcal (Fresenius Kabi)	Liquid (sip feed) per 100 mL	840 kJ (200 kcal)	10 g cows' milk	22.5 g (sugars 5.8 g ¹)	7.8 g	Nil	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis	Bottle: 200 mL = £1.91 Apricot-peach, cappuccino, fruits of the forest, neutral, toffee, vanilla
Fresubin® 2 kcal Fibre (Fresenius Kabi)	Liquid (sip feed) per 100 mL	840 kJ (200 kcal) ²	10 g cows' milk	22.5 g (sugars 5.8 g)	7.8 g	1.6 g	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis	Bottle: 200 mL = £1.91 Apricot-peach, cappuccino, chocolate, lemon, neutral, vanilla
Fresubin® Crème (Fresenius Kabi)	Semi-solid per 100 g	775 kJ (185 kcal) ²	10 g cows' milk	19 g (sugars 14.4 g)	7.2 g	2 g	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis Not suitable for child under 3 years	Pot: 4 × 125 g = £7.72 Cappuccino, chocolate, praline, strawberry, vanilla
Fresubin® Powder Extra (Fresenius Kabi)	Powder per 100 g	1764 kJ (420 kcal) ²	17.5 g cows' milk whey protein	63 g (sugars 24.7 g)	10.9 g	Nil	Gluten-free Contains lactose	Standard, p. 771	Sachet: 7 × 62 g = £5.60 Chocolate, neutral, strawberry, vanilla
Powder 62 g reconstituted with 200 mL whole milk provides: protein 17.7 g, carbohydrate 48.5 g, fat 14.8 g, energy 1658 kJ (397 kcal)									
Nutilis® Complete Stage 1 (Nutricia Clinical)	Liquid (pre-thickened) per 100 mL	1010 kJ (240 kcal)	9.6 g cows' milk	29.1 g (sugars 5.4 g)	9.3 g	3.2 g	Residual lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 125 mL = £2.10 Strawberry, vanilla
Nutilis® Complete Stage 2 (Nutricia Clinical)	Semi-solid per 100 g	1030 kJ (245 kcal) ²	9.6 g cows' milk	29.1 g (sugars 11.8 g)	9.4 g	3.2 g	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 3 years; use with caution in child 3– 6 years	Pot: 4 × 125 g = £8.84 Strawberry, vanilla
Nutricrem® (Nualtra)	Semi-solid per 100 g	756 kJ (180 kcal)	10 g cows' milk soya protein	18.8 g (sugars 9.7 g)	7.2 g	Nil	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 3 years; use with caution in child 3– 6 years	Pot: 4 × 125 g = £5.60 Strawberry, vanilla
Nutriplen® (Nualtra)	Liquid (sip feed) per 100 mL	1008 kJ (240 kcal)	9.6 g cows' milk soya protein	28.8 g (sugars 11.6 g) ¹	9.6 g	Nil	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 3 years; use with caution in child 3– 6 years	Bottle: 4 × 125 mL = £5.80 Strawberry, vanilla
Renilon® 7.5 (Nutricia Clinical)	Liquid (sip feed) per 100 mL	840 kJ (200 kcal)	7.5 g cows' milk	20 g (sugars 4.8 g)	10 g	Nil	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 3 years	Bottle: 4 × 125 mL = £8.24 Apricot, caramel
Resource® 2.0 Fibre (Nestlé)	Liquid (sip feed) per 100 mL	836 kJ (200 kcal) ²	9 g cows' milk	21.4 g (sugars 5.5 g)	8.7 g	2.5 g	Gluten-free Residual lactose	Standard, p. 771 Not suitable for child under 6 years; caution in child 6–10 years	Carton: 200 mL = £1.88 Apricot, coffee, neutral, strawberry, summer fruits, vanilla

1. Sugar content varies with flavour

2. Nutritional values vary with flavour—consult product literature

A2.2.2.3 Nutritional supplements: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL (*product list continued*)

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Resource® Dessert Fruit (Nestlé)	Semi-solid per 100 g	678 kJ (160 kcal) ¹	5 g cows' milk	24 g (sugars 16.4 g)	5 g	1.4 g	Gluten-free Residual lactose	Standard, p. 771; <i>also</i> CAPD, haemodialysis	Cup: 3 × 125 g = £4.77 Apple, apple-peach, apple-strawberry ²
Vegenat-med® Balanced Protein (Vegenat)	Powder per 110 g serving	1924 kJ (458 kcal) ¹	18 g cows' milk	62 g	15.35 g	5.8 g	Gluten-free Residual lactose	Standard, p. 771 except bowel fistula Not suitable for child under 14 years	Sachet: 12 × 110 g = £36.26 Apple, chocolate, honey, orange
Vegenat-med® High Protein (Vegenat)	Powder per 110 g serving	1940 kJ (463 kcal) ¹	23.3 g cows' milk	57.2 g	15.6 g	6 g	Gluten-free Residual lactose	Standard, p. 771 except bowel fistula Not suitable for child under 14 years	Sachet: 12 × 110 g = £50.76 Chicken, chickpea, fish, fish-vegetable, ham, lentil, veal, vegetable, winter vegetable 12 × 110 g = £48.95 Curry chicken 12 × 110 g = £48.22 Lemon, rice with lemon 24 × 55 g = £46.50 Rice with apple

1. Nutritional values vary with flavour—consult product literature

2. Flavour not suitable for child under 3 years

A2.3 Specialised formulas

A2.3.1 Specialised formulas: Infant and child

Specialised formulas are suitable for infants from birth unless otherwise indicated (*see also* A2.1.3.1 Enteral feeds (non-disease specific): Child under 12 years)

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Specialised formulas: Infant and child: Amino acid-based formula									
ACBS Indications: Proven whole protein intolerance, short bowel syndrome, intractable malabsorption, or other gastro-intestinal disorders where an elemental diet is indicated									
Neocate [®] Active (SHS)	Standard dilution (21%) of powder per 300 mL serving (63-g sachet made up to 300 mL with water)	1255 kJ (300 kcal)	8.3 g protein equivalent (essential and non-essential amino acids)	34 g (sugars 3.1 g ¹)	14.5 g	Nil	Milk protein-free	See above Nutritional supplement only Not suitable for child under 1 year	Sachet: 15 × 63 g = £66.60 Black currant, unflavoured ²
Powder provides: protein equivalent 13.1 g, carbohydrate 54 g, fat 23 g, energy 1992 kJ (475 kcal)/100 g									
Neocate [®] Advance (SHS)	Standard dilution (25%) of powder per 100 mL	420 kJ (100 kcal)	2.5 g protein equivalent (essential and non-essential amino acids)	14.6 g (sugars 1.3 g ¹)	3.5 g (MCT 35%)	Nil	Milk protein-free	See above Not suitable for child under 1 year	Sachet: 100 g = £4.94 Unflavoured ² 15 × 50 g = £46.35 Banana-vanilla
Powder provides: protein equivalent 10 g, carbohydrate 58.5 g, fat 14 g, energy 1683 kJ (400 kcal)/100 g									
Neocate [®] LCP (SHS)	Standard dilution (14.7%) of powder per 100 mL	293 kJ (70 kcal)	1.9 g protein equivalent (essential and non-essential amino acids)	7.9 g (sugars 720 mg)	3.4 g	Nil	Milk protein-free	Cows' milk allergy, multiple food protein intolerance, and conditions requiring an elemental diet	Can: 400 g = £28.30 (4.9-g measuring scoop provided)
Powder provides: protein equivalent 13 g, carbohydrate 54 g, fat 23 g, energy 1990 kJ (475 kcal)/100 g									

1. Sugar content varies with flavour

2. Flavouring: see *Modjul*[®] Flavour System, p. 807

A2.3.1 Specialised formulas: Infant and child (*product list continued*)Specialised formulas are suitable for infants from birth unless otherwise indicated (*see also* A2.1.3.1 Enteral feeds (non-disease specific): Child under 12 years)

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Neocate [®] Spoon (Nutricia Clinical)	Standard dilution (38 %) of powder per 97 g serving (37-g sachet diluted with 60 mL water)	733 kJ (175 kcal)	3 g protein equivalent (essential and non- essential amino acids)	24.9 g (sugars 4.6 g)	7 g	Nil	Milk protein-free	Cows' milk allergy, multiple food protein intolerance, and conditions requiring an elemental diet Not suitable for child under 6 months	Sachet: 15 × 37 g = £39.30
Powder provides protein equivalent 8.2 g, carbohydrate 67.4 g, fat 18.8 g, energy 1981 kJ (472 kcal)/100 g									
Nutramigen [®] AA (Mead Johnson)	Standard dilution (13.6 %) of powder per 100 mL	286 kJ (68 kcal)	1.89 g essential and non- essential amino acids	7 g	3.6 g	Nil	Gluten-free Lactose-free	Severe cows' milk protein intolerance, or multiple food intolerance, and other gastro- intestinal disorders where an elemental diet is specifically indicated	Can: 400 g = £25.58 (4.5-g measuring scoop provided)
Powder provides: protein 13.9 g, carbohydrate 51 g, fat 26 g, energy 2092 kJ (498 kcal)/100 g									
Specialised formulas: Infant and child: Hydrolysate formula									
Althéra [®] (Vitafo)	Standard dilution (13.2%) of powder per 100 mL	280 kJ (67 kcal)	1.7 g whey hydrolysed	7.3 g (sugars 4 g)	3.4 g	Nil	Contains lactose	Complete nutritional support from birth to 3 years or supplementary feeding from 6 months to 3 years, in cow's milk protein allergy or multiple food protein allergies	Can: 450 g = £10.68 (4.4-g measuring scoop provided)
Powder provides: protein 12.5 g, carbohydrate 55.5 g, fat 26 g, energy 2117 kJ (506 kcal)/100 g									
Aptamil Pepti [®] 1 (Allergy) (Milupa)	Standard dilution (13.6 %) of powder per 100 mL	280 kJ (67 kcal)	1.6 g whey hydrolysed	7.1 g (sugars 3.5 g)	3.5 g	600 mg	Contains lactose and fish oil	Established cows' milk protein intolerance, with or without secondary lactose intolerance	Can: 400 g = £9.54 900 g = £21.46 (4.5-g measuring scoop provided)
Formerly Aptamil Pepti [®] Powder provides: protein 11.6 g, carbohydrate 52 g, fat 25.6 g, energy 2025 kJ (484 kcal)/100 g									
Aptamil Pepti [®] 2 (Allergy) (Milupa)	Standard dilution (14.3 %) of powder per 100 mL	285 kJ (68 kcal)	1.6 g	8 g (sugars 3.6 g)	3.1 g	600 mg	Contains lactose and fish oil	Established cows' milk protein allergy or intolerance Not suitable for child under 6 months	Can: 900 g = £20.48 (4.8-g measuring scoop provided)
Powder provides: protein 11.2 g, carbohydrate 56.1 g, fat 21.8 g, energy 1985 kJ (473 kcal)/100 g									

Cow & Gate Pepti-Junior® (Cow & Gate)	Standard dilution (12.8 %) of powder per 100 mL	275 kJ (66 kcal)	1.8 g whey hydrolysed	6.8 g (sugars 1.1 g)	3.5 g	Nil	Residual lactose Contains fish oil	Disaccharide and/or whole protein intolerance, or where amino acids and peptides are indicated in conjunction with medium chain triglycerides	Can: 450 g = £12.58 (4.3-g measuring scoop provided)
Powder provides: protein 14 g, carbohydrate 53.4 g, fat 27.3 g, energy 2155 kJ (515 kcal)/100 g									
Infatrin® Peptisorb (Nutricia Clinical)	Liquid (sip or tube feed) per 100 mL	420 kJ (100 kcal)	2.6 g whey protein hydrolysate	10.3 g (sugars 2.7 g)	5.4 g (MCT 50%)	Nil	Gluten-free Residual lactose Contains fish oil	Disease-related malnutrition, intractable malabsorption, proven inflammatory bowel disease, short bowel syndrome, bowel fistula, and intolerance to whole protein feeds in child from birth to 18 months or body-weight up to 9 kg	Bottle: 200 mL = £3.32
Nutramigen® Lipil 1 (Mead Johnson)	Standard dilution (13.5 %) of powder per 100 mL	280 kJ (68 kcal)	1.9 g casein hydrolysed	7.5 g	3.4 g	Nil	Gluten-free Lactose-free	Disaccharide and/or whole protein intolerance where additional medium chain triglycerides are not included	Can: 400 g = £10.38 (4.5-g measuring scoop provided)
Powder provides: protein 14 g, carbohydrate 55 g, fat 25 g, energy 2100 kJ (500 kcal)/100 g									
Nutramigen® Lipil 2 (Mead Johnson)	Standard dilution (14.6 %) of powder per 100 mL	285 kJ (68 kcal)	1.7 g casein hydrolysed	8.6 g	2.9 g	Nil	Gluten-free Lactose-free	Established disaccharide and/or whole protein intolerance (where additional chain triglycerides are not indicated) Not suitable for child under 6 months	Can: 400 g = £10.38 (4.9-g measuring scoop provided)
Powder provides: protein 11.6 g, carbohydrate 59 g, fat 20 g, energy 1950 kJ (466 kcal)/100 g									
Pepdite® (SHS)	Standard dilution (15 %) of powder per 100 mL	297 kJ (71 kcal)	2.1 g protein equivalent (non-milk hydrolysate)	7.8 g (sugars 700 mg)	3.5 g	Nil	Lactose-free Contains meat (pork) and soya derivatives	Disaccharide and/or whole protein intolerance	Can: 400 g = £17.89 (5-g measuring scoop provided)
Powder provides: protein equivalent 13.8 g, carbohydrate 52 g, fat 23.2 g, energy 1977 kJ (472 kcal)/100 g									

A2.3.1 Specialised formulas: Infant and child (*product list continued*)Specialised formulas are suitable for infants from birth unless otherwise indicated (*see also* A2.1.3.1 Enteral feeds (non-disease specific): Child under 12 years)

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Peptide® 1+ (SHS)	Standard dilution (22.8%) of powder per 100 mL	423 kJ (100 kcal)	3.1 g protein equivalent (non-milk hydrolysate, essential amino acids)	13 g (sugars 1.2 g)	3.9 g (MCT 35%)	Nil	Lactose-free Contains meat (pork) and soya derivatives	Disaccharide and/or whole protein intolerance, or where amino acids or peptides are indicated in conjunction with medium chain triglycerides Not suitable for child under 1 year	Can: 400 g = £18.78 Unflavoured ¹
Powder provides: protein equivalent 13.8 g, carbohydrate 57 g, fat 17.3 g, energy 1844 kJ (439 kcal)/100 g									
Pregestimil® Lipil (Mead Johnson)	Standard dilution (13.5%) of powder per 100 mL	280 kJ (68 kcal)	1.89 g casein hydrolysed	6.9 g	3.8 g (MCT 54%)	Nil	Gluten-free Lactose-free	Disaccharide and/or whole protein intolerance, or where amino acids or peptides are indicated in conjunction with medium chain triglycerides	Can: 400 g = £11.51 (4.5-g measuring scoop provided)
Powder provides: protein 14 g, carbohydrate 51 g, fat 28 g, energy 2100 kJ (500 kcal)/100 g									
Similac® Alimentum (Abbott)	Standard dilution (14%) of powder per 100 mL	283 kJ (67.6 kcal)	1.86 g casein hydrolysed	6.62 g (sugars 1.5 g)	3.75 g (MCT 33%)	Nil	Gluten-free Lactose-free Contains meat derivatives	Cows' milk protein allergy and other conditions where an extensively hydrolysed formula is indicated	Can: 400 g = £9.10 (4.2-g measuring scoop provided)
Powder provides: protein 14.4 g, carbohydrate 51.4 g, fat 29.1 g, energy 2196 kJ (525 kcal)/100 g									
Specialised formulas: Infant and child: Residual lactose formula									
Enfamil® O-Lac (Mead Johnson)	Standard dilution (13%) of powder per 100 mL	280 kJ (68 kcal)	1.42 g cows' milk	7.2 g	3.7 g	Nil	Gluten-free Residual lactose	Proven lactose intolerance	Can: 400 g = £4.70 (4.3-g measuring scoop provided)
Powder provides: protein 10.9 g, carbohydrate 55 g, fat 28 g, energy 2200 kJ (524 kcal)/100 g									
Galactomin 17® (SHS)	Standard dilution (13.6%) of powder per 100 mL	295 kJ (70 kcal)	1.7 g protein equivalent (cows' milk)	7.5 g (sugars 1.4 g)	3.7 g	Nil	Residual lactose	Proven lactose intolerance in pre-school children, galactosaemia, and galactokinase deficiency	Can: 400 g = £16.01 Unflavoured ¹ (4.3-g measuring scoop provided)
Powder provides: protein equivalent 12.3 g, carbohydrate 55.3 g, fat 27.2 g, energy 2155 kJ (515 kcal)/100 g									
SMA® LF (SMA Nutrition)	Standard dilution (13%) of powder per 100 mL	281 kJ (67 kcal)	1.5 g casein, whey	7.2 g (sugars 2.6 g)	3.6 g	Nil	Residual lactose	Proven lactose intolerance	Can: 430 g = £5.06.
Powder provides: protein 12 g, carbohydrate 55.6 g, fat 28 g, energy 2185 kJ (522 kcal)/100 g									

1. Flavouring: see *Modjui*® Flavour System, p. 807

Specialised formulas: Infant and child: MCT-enhanced formula

Caprilon® (SHS)	Standard dilution (12.7 %) of powder per 100 mL	277 kJ (66 kcal)	1.5 g cows' milk	7 g (sugars 1.3 g)	3.6 g (MCT 75 %)	Nil	Contains lactose	Disorders in which a high intake of MCT is beneficial	Can: 420 g = £17.36 (4.2-g measuring scoop provided)
Powder provides: protein 11.8 g, carbohydrate 55.1 g, fat 28.3 g, energy 2184 kJ (522 kcal)/100 g									
Lipistart® (Vitafo)	Standard dilution (15 %) of powder per 100 mL	282 kJ (68 kcal)	2.1 g protein equivalent (whey, soya)	8.3 g (sugars 700 mg)	3.1 g (MCT 81 %)	Nil	Residual lactose	Dietary management of fat malabsorption, long-chain fatty acid oxidation disorders, and other disorders requiring a high MCT, low LCT formula	Can: 400 g = £18.67 (5-g measuring scoop provided)
Powder provides: protein equivalent 13.7 g, carbohydrate 55.3 g, fat 20.6 g, energy 1883 kJ (450 kcal)/100 g									
MCT Peptide® (SHS)	Standard dilution (15 %) of powder per 100 mL	286 kJ (68 kcal)	2 g protein equivalent (non-milk peptides, essential amino acids)	8.8 g (sugars 1.2 g)	2.7 g (MCT 75 %)	Nil	Gluten-free Lactose-free Contains meat (pork) and soya derivatives	Disorders in which a high intake of MCT is beneficial	Can: 400 g = £19.47 (5-g measuring scoop provided)
Powder provides: protein equivalent 13.8 g, carbohydrate 59 g, fat 18 g, energy 1903 kJ (453 kcal)/100 g									
MCT Peptide® +1 (SHS)	Standard dilution (20 %) of powder per 100 mL	381 kJ (91 kcal)	2.8 g protein equivalent (non-milk peptides, essential amino acids)	11.8 g (sugars 1.6 g)	3.6 g (MCT 75 %)	Nil	Gluten-free Lactose-free Contains meat (pork) and soya derivatives	Disorders in which a high intake of MCT is beneficial Not suitable for child under 1 year	Can: 400 g = £19.47 Unflavoured ¹
Powder provides: protein equivalent 13.8 g, carbohydrate 59 g, fat 18 g, energy 1903 kJ (453 kcal)/100 g									
Monogen® (SHS)	Standard dilution (17.5 %) of powder per 100 mL	310 kJ (74 kcal)	2.2 g protein equivalent (whey)	12 g (sugars 1.2 g)	1.9 g (MCT 80 %)	Nil	Residual lactose Supplementation with essential fatty acids may be needed	Long-chain acyl-CoA dehydrogenase deficiency (LCAD), carnitine palmitoyl transferase deficiency (CPTD), primary and secondary lipoprotein lipase deficiency, chylothorax, and lymphangiectasia	Can: 400 g = £19.35 Unflavoured ¹ (5-g measuring scoop provided)
Powder provides: protein equivalent 12.5 g, carbohydrate 68 g, fat 11 g, energy 1769 kJ (420 kcal)/100 g									

1. Flavouring: see *Modjul*® Flavour System, p. 807

A2.3.1 Specialised formulas: Infant and child (*product list continued*)Specialised formulas are suitable for infants from birth unless otherwise indicated (*see also* A2.1.3.1 Enteral feeds (non-disease specific): Child under 12 years)

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Specialised formulas: Infant and child: Soya-based formula									
Infasoy® (Cow & Gate)	Standard dilution (12.8%) of powder per 100 mL	275 kJ (66 kcal)	1.6 g soya	7 g (sugars 1 g)	3.5 g	Nil	Lactose-free	Proven lactose and associated sucrose intolerance in pre-school children, galactokinase deficiency, galactosaemia, and proven whole cows' milk sensitivity	Can: 900 g = £8.14 (4.3-g measuring scoop provided)
Powder provides: protein 12.8 g, carbohydrate 54.5 g, fat 27.3 g, energy 2150 kJ (514 kcal)/100 g									
Wysoy® (Wyeth)	Standard dilution (13.2%) of powder per 100 mL	280 kJ (67 kcal)	1.8 g soya protein isolate	6.9 g (sugars 2.5 g)	3.6 g	Nil	Lactose-free	Proven lactose and associated sucrose intolerance in pre-school children, galactokinase deficiency, galactosaemia, and proven whole cows' milk sensitivity	Can: 430 g = £5.05 860 g = £9.62
Powder provides: protein 14 g, carbohydrate 54 g, fat 27 g, energy 2155 kJ (515 kcal)/100 g									
Specialised formulas: Infant and child: Low calcium formula									
Locasol® (SHS)	Standard dilution (13.1%) of powder per 100 mL	278 kJ (66 kcal)	1.9 g cows' milk	7 g (sugars 6.9 g)	3.4 g	Nil	Contains lactose Calcium less than 7 mg/ 100 mL No added vitamin D	Conditions of calcium intolerance requiring restriction of calcium and vitamin D intake	Can: 400 g = £22.25 (4.4-g measuring scoop provided)
Powder provides: protein 14.6 g, carbohydrate 53.7 g, fat 26.1 g, energy 2125 kJ (508 kcal)/100 g									
Specialised formulas: Infant and child: Fructose-based formula									
Galactomin 19® (SHS)	Standard dilution (12.9%) of powder per 100 mL	288 kJ (69 kcal)	1.9 g protein equivalent (cows' milk)	6.4 g (fructose 6.3 g)	4 g	Nil	Residual lactose, galactose and glucose	Conditions of glucose plus galactose intolerance	Can: 400 g = £42.15
Powder provides: protein equivalent 14.6 g, carbohydrate 49.7 g, fat 30.8 g, energy 2233 kJ (534 kcal)/100 g									

Specialised formulas: Infant and child: Pre-thickened infant feeds

Note Not to be used for a period of more than 6 months; not to be used in conjunction with any other feed thickener or antacid products

Enfamil® AR (Mead Johnson)	Standard dilution (13.5%) of powder per 100 mL	285 kJ (68 kcal)	1.7 g cows' milk	7.6 g (lactose 4.6 g)	3.5 g	Nil	Contains lactose, pregelatinised rice starch	Significant gastro-oesophageal reflux	Can: 400 g = £3.52 (4.5-g measuring scoop provided)
Powder provides: protein 12.5 g, carbohydrate 56 g, fat 26 g, energy 2093 kJ (500 kcal)/100 g									
SMA® Staydown (SMA Nutrition)	Standard dilution (12.9%) of powder per 100 mL	279 kJ (67 kcal)	1.6 g casein, whey	7 g (lactose 5 g)	3.6 g	Nil	Contains lactose, pre- cooked corn starch	Significant gastro-oesophageal reflux	Can: 900 g = £7.29
Powder provides: protein 12.4 g, carbohydrate 54.3 g, fat 28 g, energy 2166 kJ (518 kcal)/100 g									

A2.3.2 Specialised formulas for specific clinical conditions

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Alicalm® (SHS)	Standard dilution (30%) of powder per 100 mL	567 kJ (135 kcal)	4.5 g caseinate whey	17.4 g (sugars 3.2 g)	5.3 g	Nil	Residual lactose	Crohn's disease Not suitable for child under 1 year; use as nutritional supplement only in children 1–6 years.	Powder: 400 g = £20.48 Vanilla
Powder provides: protein 15 g, carbohydrate 58 g, fat 17.5 g, energy 1889 kJ (450 kcal)/100 g									
Forticare® (Nutricia Clinical)	Liquid (sip feed) per 100 mL	675 kJ (160 kcal)	9 g cows' milk	19.1 g (sugars 13.6 g)	5.3 g	2.1 g	Gluten-free Residual lactose Contains fish oil	Nutritional supplement in patients with lung cancer undergoing chemotherapy, or with pancreatic cancer Not suitable in child under 3 years	Bottle: 4 × 125 mL = £8.84 Cappuccino, orange-lemon, peach-ginger
Generaid® (SHS)	Powder per 100 g	1586 kJ (374 kcal)	76 g protein equivalent (whey protein, plus branched chain amino acids)	5 g (sugars 5 g)	5.5 g	Nil	Electrolytes/100 g: Na ⁺ 6.1 mmol K ⁺ 10.8 mmol Ca ²⁺ 6.5 mmol P ⁺ 6.45 mmol	Nutritional supplement for use in chronic liver disease and/or porto- hepatic encephalopathy	Tub: 400 g = £58.32 Unflavoured ¹

1. Flavouring: see *Modjul*® Flavour System, p. 807

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Generaid® Plus (SHS)	Standard dilution (22%) of powder per 100 mL	428 kJ (102 kcal)	2.4 g protein equivalent (whey protein, branched chain amino acids)	13.6 g (sugars 1.4 g)	4.2 g (MCT 32%)	Nil	Electrolytes/100 mL: Na ⁺ 0.7 mmol K ⁺ 2.7 mmol Ca ²⁺ 1.72 mmol P ⁺ 1.67 mmol	Enteral feed or nutritional supplement in children over 1 year with hepatic disorders	Can: 400 g = £20.86 Unflavoured ¹ (5-g measuring scoop provided)
Powder provides: protein equivalent 11 g, carbohydrate 62 g, fat 19 g, energy 1944 kJ (463 kcal)/100 g									
Heparon® Junior (SHS)	Standard dilution (18%) of powder per 100 mL	363 kJ (86 kcal)	2 g cows' milk	11.6 g (sugars 2.9 g)	3.6 g	Nil	Contains lactose Electrolytes/100 mL: Na ⁺ 0.56 mmol K ⁺ 1.9 mmol Ca ²⁺ 2.3 mmol P ⁺ 1.6 mmol	Enteral feed or nutritional supplement for children with acute or chronic liver failure	Can: 400 g = £20.63 (4.5-g measuring scoop provided)
Powder provides: protein 11.1 g, carbohydrate 64.2 g, fat 19.9 g, energy 2016 kJ (480 kcal)/100 g									
KetoCal® (SHS)	Standard dilution (20%) of powder per 100 mL	602 kJ (146 kcal)	3.1 g cows' milk with additional amino acids	600 mg (sugars 120 mg)	14.6 g (LCT 100%)	Nil	Electrolytes/100 mL: Na ⁺ 4.3 mmol K ⁺ 4.1 mmol Ca ²⁺ 2.15 mmol P ⁺ 2.77 mmol	Enteral feed or nutritional supplement as part of ketogenic diet in management of epilepsy resistant to drug therapy, in children over 1 year, only on the advice of secondary care physician with experience of ketogenic diet	Can: 300 g = £29.04 Vanilla, Unflavoured
Powder provides: protein 15.25 g, carbohydrate 3 g, fat 73 g, energy 3011 kJ (730 kcal)/100 g									
KetoCal® 3:1 (SHS)	Standard dilution (9.5%) of powder per 100 mL	276 kJ (66 kcal)	1.5 g	680 mg (sugars 570 mg)	6.4 g	Nil	Electrolytes/100 mL: Na ⁺ 1.3 mmol K ⁺ 2.4 mmol Ca ²⁺ 2 mmol P ⁺ 1.7 mmol	Enteral feed or nutritional supplement as part of ketogenic diet in management of drug resistant epilepsy or other conditions for which a ketogenic diet is indicated in children from birth to 6 years; as a nutritional supplement in children over 6 years	Can: 300 g = £28.11 Unflavoured
Powder provides: protein 15.3 g, carbohydrate 7.2 g, fat 67.7 g, energy 2927 kJ (699 kcal)/100 g									

1. Flavouring: see *Modjul*[®] Flavour System, p. 807

KetoCal® 4:1 LQ (SHS)	Liquid (sip or tube feed) per 100 mL	620 kJ (150 kcal)	3.09 g casein and whey with additional amino acids	610 mg (sugars 230 mg)	14.8 g (LCT 100 %)	1.12 g	Residual lactose Electrolytes/100 mL: Na ⁺ 4.9 mmol K ⁺ 4.7 mmol Ca ²⁺ 2.4 mmol P ⁺ 3.1 mmol	Enteral feed or nutritional supplement as part of ketogenic diet in management of drug resistant epilepsy or other conditions for which a ketogenic diet is indicated in children 1–10 years; as a nutritional supplement in children over 10 years	Carton: 237 mL = £4.76 Vanilla
Kindergen® (SHS)	Standard dilution (20 %) of powder per 100 mL	421 kJ (101 kcal)	1.5 g whey protein	11.8 mg (sugars 1.2 g)	5.3 g (LCT 93 %)	Nil	Electrolytes/100 mL: Na ⁺ 2 mmol K ⁺ 0.6 mmol Ca ²⁺ 2.8 mmol P ⁺ 3 mmol Low Vitamin A	Enteral feed or nutritional supplement for children with chronic renal failure receiving peritoneal rapid overnight dialysis	Tub: 400 g = £27.69 (5-g measuring scoop provided)
Powder provides: protein 7.5 g, carbohydrate 59 g, fat 26.3 g, energy 2104 kJ (504 kcal)/100 g									
Modulen IBD® (Nestlé)	Standard dilution (20%) of powder (sip or tube feed) per 100 mL	420 kJ (100 kcal)	3.6 g casein	11 g (sugars 3.98 g)	4.7 g	Nil	Gluten-free Residual lactose	Crohn's disease active phase, and in remission if malnourished	Can: 400 g = £15.06 Unflavoured ¹ (8.3-g measuring scoop provided)
Powder provides: protein 18 g, carbohydrate 54 g, fat 23 g, energy 2070 kJ (500 kcal)/100 g									
Nepro® (Abbott)	Liquid (sip or tube feed) per 100 mL	838 kJ (200 kcal) ²	7 g cows' milk	20.6 g (sugars 3.26 g)	9.6 g	1.56 g	Gluten-free Residual lactose Electrolytes/100 mL: Na ⁺ 3.67 mmol K ⁺ 2.72 mmol Ca ²⁺ 3.43 mmol P ⁺ 2.23 mmol	Enteral feed or nutritional supplement in patients with chronic renal failure who are on haemodialysis or CAPD, or with cirrhosis, or other conditions requiring a high energy, low fluid, low electrolyte diet. Not suitable for child under 1 year; use with caution in child 1–5 years	Carton: 200 mL = £2.69 Strawberry, vanilla Flexible pack: 500 mL = £5.84 Vanilla
1. Flavouring: see <i>Flavour Mix</i> ®, p. 807 2. Nutritional values vary with flavour—consult product literature									

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
ProSure® (Abbott)	Liquid (sip or tube feed) per 100 mL	536 kJ (127 kcal) ¹	6.65 g cows' milk	18.3 g (sugars 2.95 g)	2.56 g	2.07 g	Gluten-free Residual lactose Contains fish oil	Nutritional supplement for patients with pancreatic cancer Not suitable for child under 1 year; use with caution in child 1–4 years	Carton: 240 mL = £3.29 Vanilla
Renamil® (KoRa)	Powder (sip or tube feed when reconstituted) per 100 g	2003 kJ (477 kcal)	4.6 g cows' milk	70.8 g	19.3 g	Nil	Contains lactose Gluten-free Electrolytes/100 g: Na ⁺ 1.04 mmol K ⁺ 0.13 mmol Ca ²⁺ 10.22 mmol P ⁺ 1.06 mmol Contains no vitamin A or vitamin D	Enteral feed or nutritional supplement for adults and children over 1 year with chronic renal failure	Sachet: 10 × 100 g = £25.40
Renapro® (KoRa)	Powder per 100 g	1580 kJ (372 kcal)	90 g whey protein	800 mg	1 g	Nil	Gluten-free Residual lactose Electrolytes/100 g: Na ⁺ 23 mmol K ⁺ 2 mmol Ca ²⁺ 4.99 mmol P ⁺ 4.84 mmol	Nutritional supplement for biochemically proven hypoproteinaemia and patients undergoing dialysis Not suitable for child under 1 year	Sachet: 30 × 20 g = £69.60
Powder provides: protein 18 g, energy 316 kJ (74 kcal)/20-g sachet									
Renastart® (Vitaflo)	Standard dilution (20%) of powder per 100 mL	414 kJ (99 kcal)	1.5 g cows' milk soya	12.5 g (sugars 1.3 g)	4.8 g	Nil	Contains lactose Electrolytes/100 mL: Na ⁺ 2.1 mmol K ⁺ 0.6 mmol Ca ²⁺ 0.6 mmol P ⁺ 0.6 mmol	Dietary management of renal failure in child from birth to 10 years	Can: 400 g = £25.42 Unflavoured (7-g measuring scoop provided)
Powder provides: protein 7.5 g, carbohydrate 62.5 g, fat 23.8 g, energy 2071 kJ (494 kcal)/100 g									
Suplena® (Abbott)	Liquid (sip or tube feed) per 100 mL	840 kJ (200 kcal)	3 g caseinates	25.5 g (sugars 2.7 g)	9.6 g	Nil	Gluten-free Residual lactose Electrolytes/100 mL: Na ⁺ 3.39 mmol K ⁺ 2.87 mmol Ca ²⁺ 3.48 mmol P ⁺ 2.39 mmol	Enteral feed or nutritional supplement in patients with chronic or acute renal failure who are not undergoing dialysis, or with chronic or acute liver disease with fluid restriction; other conditions requiring high energy, low protein, low electrolyte, low volume enteral feed Not suitable for child under 1 year; use with caution in child 1–5 years	Can: 237 mL = £2.85 Vanilla

1. Nutritional values vary with flavour—consult product literature

A2.4 Feed supplements

A2.4.1 High-energy supplements

A2.4.1.1 High-energy supplements: carbohydrate

Flavoured carbohydrate supplements are not suitable for child under 1 year; liquid supplements should be diluted before use in child under 5 years

ACBS Indications: disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Caloreen® (Nestlé)	Powder per 100 g	1640 kJ (390 kcal)	Nil	96 g Maltodextrin	Nil	Nil	Gluten-free Lactose-free	See above Not suitable for child under 3 years	Powder: 500 g = £3.69 Unflavoured (10-g measuring scoop provided)
Maxijul® Super Soluble (SHS)	Powder per 100 g	1615 kJ (380 kcal)	Nil	95 g Glucose polymer (sugars 8.6 g)	Nil	Nil	Gluten-free Lactose-free	See above	Sachets: 4 × 132 g = £6.16 Can: 200 g = £2.48 2.5 kg = £19.25 25 kg = £148.21 Unflavoured
Polycal® (Nutricia Clinical)	Powder per 100 g	1630 kJ (384 kcal)	Nil	96 g Maltodextrin (sugars 6 g)	Nil	Nil	Gluten-free Lactose-free	See above	Can: 400 g = £4.09 Neutral (5-g measuring scoop provided)
	Liquid per 100 mL	1050 kJ (247 kcal)	Nil	61.9 g Maltodextrin (sugars 12.2 g)	Nil	Nil		See above; liquid not suitable for child under 3 years	Bottle: 200 mL = £1.64 Neutral, orange
S.O.S.® (Vitafo)	Powder per 100 g	1590 kJ (380 kcal)	Nil	95 g (sugars 9 g)	Nil	Nil		For use as an emergency regimen in the dietary management of inborn errors of metabolism in adults and children from birth	Sachets ¹ : 30 × 21 g (S.O.S. 10) = £7.05; 30 × 31 g (S.O.S. 15) = £10.40; 30 × 42 g (S.O.S. 20) = £14.09; 30 × 52 g (S.O.S. 25) = £17.44
Contents of each sachet should be reconstituted with water to a total volume of 200 mL									
Vitajoule® (Vitafo)	Powder per 100 g	1590 kJ (380 kcal)	Nil	95 g Dried glucose syrup (sugars 9 g)	Nil	Nil	Gluten-free Lactose-free	See above	Can: 500 g = £4.22 2.5 kg = £20.54 25 kg = £123.70 (10-g measuring scoop provided)

1. S.O.S. products are age-range specific—consult product literature

A2.4.1.2 High-energy supplements: fat

Liquid supplements should be diluted before use in child under 5 years

ACBS indications: disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Calogen® (Nutricia Clinical)	Liquid (emulsion) per 100 mL	1850 kJ (450 kcal) ¹	Nil	100 mg	50 g (LCT 100%)	Nil	Gluten-free Lactose-free	See above	Bottle: 200 mL = £4.36 500 mL = £10.72 Banana ² , neutral, strawberry ²
Fresubin® 5 kcal Shot (Fresenius Kabi)	Liquid (emulsion) per 100 mL	2100 kJ (500 kcal)	Nil	4.0 g (sucrose)	53.8 g	400 mg	Gluten-free Lactose-free	See above Not suitable for child under 3 years	Bottle: 120 mL = £2.55 Lemon, neutral
Liquigen® (SHS)	Liquid (emulsion) per 100 mL	1850 kJ (450 kcal)	Nil	Nil	50 g (MCT 97%) Fractio- nated coco- nut oil	Nil	Gluten-free Lactose-free	Steatorrhoea associated with cystic fibrosis of the pancreas, intestinal lymphangiectasia, intestinal surgery, chronic liver disease, liver cirrhosis, other proven malabsorption syndromes, ketogenic diet in epilepsy, and in type 1 lipoproteinaemia Not suitable for child under 1 year	Bottle: 250 mL = £8.83
Medium-chain Triglyceride (MCT) Oil (Nutricia Clinical)	Liquid per 100 mL	3515 kJ (855 kcal)	Nil	Nil	MCT 100%	Nil		Nutritional supplement for steatorrhoea associated with cystic fibrosis of the pancreas, intestinal lymphangiectasia, intestinal surgery, chronic liver disease and liver cirrhosis, other proven malabsorption syndromes, ketogenic diet in management of epilepsy, type 1 hyperlipoproteinaemia	Bottle: 500 mL = £13.99
Fat and Carbohydrate									
Duocal® Super Soluble (SHS)	Powder per 100 g	2061 kJ (492 kcal)	Nil	72.7 g (sugars 6.5 g)	22.3 g (MCT 35%)	Nil	Gluten-free Lactose-free	See above	Can: 400 g = £17.23 (5-g measuring scoop provided)

1. Nutritional values vary with flavour—consult product literature

2. Flavour not suitable for child under 3 years

Energivit® (SHS)	Standard dilution (15%) of powder per 100 mL	309 kJ (74 kcal)	Nil	10 g (sugars 900 mg)	3.75 g	Nil	Lactose-free With vitamins, minerals, and trace elements	For children requiring additional energy, vitamins, minerals, and trace elements following a protein- restricted diet	Can: 400 g = £20.95 (5-g measuring scoop provided)
Powder provides: carbohydrate 66.7 g, fat 25 g, energy 2059 kJ (492 kcal)/100 g									
MCT Duocal® (SHS)	Powder per 100 g	2082 kJ (497 kcal)	Nil	72 g (sugars 10.1 g)	23.2 g (MCT 83%)	Nil		See above	Can: 400 g = £18.07

A2.4.1.3 High-energy supplements: protein

ACBS indications: disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
ProSource® Jelly (Nutrinovo)	Semi-solid per 100 mL	315 kJ (75 kcal)	16.9 g collagen protein hydrolysate whey protein isolate	Less than 1 g	Nil	Less than 1 g	Gluten-free Lactose-free Contains porcine derivatives	Hypoproteinaemia Not recommended for child under 3 years	Cup: 118 mL = £1.74 Fruit punch, orange
Protifar® (Nutricia Clinical)	Powder per 100 g	1580 kJ (373 kcal)	88.5 g cows' milk	less than 1.5 g	1.6 g	Nil	Gluten-free Residual lactose Electrolytes/100 mL: Na ⁺ 1.3 mmol K ⁺ 1.28 mmol Ca ²⁺ 33.75 mmol P ⁺ 22.58 mmol	Nutritional supplement for use in biochemically proven hypoproteinaemia	Can: 225 g = £8.31 Unflavoured (2.5-g measuring scoop provided)
Powder provides: protein 2.2 g per 2.5 g									
Vitapro® (Vitafo)	Powder per 100 g	1632 kJ (390 kcal)	75 g whey protein isolate	9 g (sugars 9 g)	6 g	Nil	Contains lactose	Biochemically proven hypoproteinaemia	Tub: 250 g = £8.60 2 kg = £67.60 (5-g measuring scoop provided)

A2.4.1.3 High-energy supplements: protein (*product list continued*)**ACBS indications:** disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Protein and carbohydrate									
Dialamine® (SHS)	Standard dilution (20%) of powder per 100 mL	264 kJ (62 kcal)	4.3 g protein equivalent (essential and non-essential amino acids)	11.2 g (sugars 10.2 g)	Nil	Nil	Contains vitamin C	Hypoproteinaemia, chronic renal failure, wound fistula leakage with excessive protein loss, conditions requiring a controlled nitrogen intake, and haemodialysis Not suitable for child under 6 months	Can: 400 g = £69.99 Orange
Powder provides: protein equivalent 25 g, carbohydrate 65 g, vitamin C 125 mg, energy 1530 kJ (360 kcal)/100 g									
ProSource® Liquid (Nutrinovo)	Liquid per 30 mL	420 kJ (100 kcal)	10 g collagen protein whey protein isolate	15 g (sugars 8 g)	Nil	Nil	Gluten-free Lactose-free May contain porcine derivatives	Biochemically proven hypoproteinaemia Not recommended for child under 3 years	Sachet: 100 × 30 mL = £94.19 Citrus-berry, neutral, orange creme
Protein, fat, and carbohydrate									
Calogen® Extra (Nutricia Clinical)	Liquid per 100 mL	1650 kJ (400 kcal) ¹	5 g cows' milk	4.5 g (sugars 3.5 g)	40.3 g	Nil	Gluten-free Residual lactose Contains vitamins and minerals	See above Not suitable for child under 3 years; use with caution in child 3–6 years May require dilution for child 3–5 years	Bottle: 200 mL = £4.98 Neutral, strawberry
Calogen® Extra Shots (Nutricia Clinical)	Liquid per 100 mL	1650 kJ (400 kcal) ¹	5 g cows' milk	4.5 g (sugars 3.5 g)	40.3 g	Nil	Gluten-free Residual lactose With vitamins and minerals	See above Not suitable for child under 3 years; use with caution in child 3–6 years May require dilution for child 3–5 years	Pot: 6 × 40 mL = £5.75 Neutral, strawberry
Calshake® (Fresenius Kabi)	Powder per 87 g	1841 kJ (439 kcal) ¹	4.1 g cows' milk	56.4 g (sugars 20 g)	22 g	Nil	Contains lactose Gluten-free	See above Not suitable for child under 1 year	Sachet: 87 g = £2.01 Banana, neutral, strawberry, vanilla 90 g = £2.01 Chocolate
Powder: one sachet reconstituted with 240 mL whole milk provides approx. 2 kcal/mL and protein 12 g									
1. Nutritional values vary with flavour—consult product literature									

Enshake® (Abbott)	Powder per 100 g	1893 kJ (450 kcal) ¹	8.4 g cows' milk, soy protein isolate	69 g (sugars 14.5 g)	15.6 g	Nil	Residual lactose Contains vitamins and minerals	See above Not suitable for child under 1 year; use with caution in child 1–6 years	Sachet: 96.5 g = £1.98 Banana, chocolate, strawberry, vanilla
Powder: 96.5 g reconstituted with 240 mL whole milk provides approx. 2 kcal/mL and protein 16 g									
MCT Procal® (Vitafo)	Powder per 100 g	2742 kJ (657 kcal)	12.5 g cows' milk	20.6 g (sugars 3.1 g)	63.1 g (MCT 99%)	Nil	Contains lactose	Dietary management of disorders of long-chain fatty acid oxidation, fat malabsorption, and other disorders requiring a low LCT, high MCT supplement Not suitable for child under 1 year	Sachet: 30 × 16 g = £22.91
Powder 16 g provides: protein 2 g, carbohydrate 3.3 g, fat 10.1 g, energy 439 kJ (105 kcal)									
Pro-Cal® (Vitafo)	Powder per 100 g	2787 kJ (667 kcal)	13.6 g cows' milk	28.2 g (sugars 16 g)	55.5 g	Nil	Contains lactose Gluten-free	See above Not suitable for child under 1 year; use with caution in child 1–5 years	Sachets: 25 × 15 g = £15.26 Tub: 510 g = £14.14 1.5 kg = £28.81 12.5 kg = £204.74 25 kg = £315.52 (15-g measuring scoop provided)
Powder 15 g provides: protein 2 g, carbohydrate 4.2 g, fat 8.3 g, energy 418 kJ (100 kcal)									
Pro-Cal® Shot (Vitafo)	Liquid per 100 mL	1385 kJ (334 kcal)	6.7 g cows' milk	13.4 g (sugars 13.3 g)	28.2 g	Nil	Contains lactose Gluten-free Contains soya	See above Not suitable for child under 3 years	Bottle: 6 × 250 mL = £26.76 Banana, neutral, strawberry Starter pack (mixed) 3 × 250 mL = £14.67
Pro-Cal® Singles (Vitafo)	Liquid per 100 mL	1385 kJ (334 kcal) ¹	6.7 g cows' milk soya	13.4 g (sugars 13.3 g)	28.2 g	Nil	Contains lactose Gluten-free	See above Not suitable for child under 3 years	Pot: 60 × 30 mL = £39.22 Neutral, strawberry Starter pack (mixed): 16 × 30 mL = £10.25
Scandishake® Mix (Nutricia Clinical)	Powder per 100 g	2099 kJ (500 kcal) ¹	4.7 g cows' milk	65 g (sugars 14.3 g)	24.7 g	Nil	Gluten-free Contains lactose	See above Not suitable for child under 3 years	Sachet: 85 g = £2.08 Banana, caramel, chocolate, strawberry, vanilla, unflavoured
Powder: 85 g reconstituted with 240 mL whole milk provides: protein 11.7 g, carbohydrate 66.8 g, fat 30.4 g, energy 2457 kJ (588 kcal)									
1. Nutritional values vary with flavour—consult product literature									

A2.4.1.3 High-energy supplements: protein (*product list continued*)**ACBS indications:** disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
Vitasavoury® (VitaFlo)	Powder per 100 g	2562 kJ (619 kcal) ¹	12 g cows' milk	22.5 g (sugars 1.4 g)	52 g	6.4 g	Contains lactose Contains soya (chicken flavour)	See above Not suitable for child under 3 years	Cup (200 kcal): 24 × 33 g = £29.97 Sachet (300 kcal): 10 × 50 g = £18.29 Chicken, leek and potato, mushroom, vegetable Starter pack (mixed): 4 × 33-g cups and 4 × 50-g sachets = £11.93

1. Nutritional values vary with flavour—consult product literature

A2.4.2 Fibre, vitamin, and mineral supplements

Product	Formulation	Energy	Protein	Carbohydrate	Fat	Fibre	Special Characteristics	ACBS Indications	Presentation & Flavour
High-fibre supplements									
Resource® Optifibre® (Nestlé)	Powder per 100 g	323 kJ (76 kcal)	Nil	19 g guar gum, partially hydrolysed	Nil	78 g	Gluten-free Lactose-free	Standard, p. 771 except dysphagia Not suitable for child under 5 years	Sachet: 16 × 10 g = £8.35 Can: 250 g = £10.28 (5-g measuring scoop provided)
Vitamin and Mineral supplements									
FruitiVits® (VitaFlo)	Powder per 100 g	133 kJ (33 kcal)	Nil	8.3 g (sugars 400 mg)	less than 100 mg	3.3 g		Vitamin, mineral, and trace element supplement in children 3–10 years with restrictive therapeutic diets	Sachets: 30 × 6 g = £61.92 Orange
Paediatric Seravit® (SHS)	Powder per 100 g	1275 kJ (300 kcal)	Nil	75 g (sugars 6.75 g ¹)	Nil	Nil		Vitamin, mineral, and trace element supplement in infants and children with restrictive therapeutic diets	Tub: 200 g = £18.17 Unflavoured ² 200 g = £17.07 Pineapple ³ (5-g measuring scoop provided)

1. Sugar content varies with flavour

2. Flavouring: see *Modjul*® Flavour System, p. 807

3. Flavour not suitable for child under 6 months

A2.5 Feed additives

A2.5.1 Special additives for conditions of intolerance

Colief® (Forum)

Liquid, lactase 50 000 units/g, net price 7-mL dropper bottle = £8.40

For the relief of symptoms associated with lactose intolerance in infants, provided that lactose intolerance is confirmed by the presence of reducing substances and/or excessive acid in stools, a low concentration of the corresponding disaccharide enzyme on intestinal biopsy or by breath hydrogen test or lactose intolerance test. For dosage and administration details, consult product literature

Fructose

(Laevulose)

For proven glucose/galactose intolerance

Glucose

(Dextrose monohydrate)

Net price 500 g = £1.48

For use as an energy supplement in sucrase-isomaltase deficiency

A2.5.2 Feed thickeners and pre-thickened drinks

Carobel, Instant® (Cow & Gate)

Powder, carob seed flour. Net price 135 g = £2.80

For thickening feeds in the treatment of vomiting

Multi-thick® (Abbott)

Powder, modified maize starch, gluten- and lactose-free, net price 250 g = £4.83

For thickening of liquids and foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive

Nutrilis® Clear (Nutricia Clinical)

Powder, maltodextrin, xanthan gum, guar gum, gluten- and lactose-free, net price 175 g = £8.46

For thickening of liquids or foods in dysphagia. Not suitable for children under 3 years

Nutrilis® Powder (Nutricia Clinical)

Powder, carbohydrate 86 g, energy 1520 kJ (358 kcal)/100 g, modified maize starch, gluten- and lactose-free, net price 20 × 9-g sachets = £5.88, 225 g = £4.51

For thickening of foods in dysphagia. Not suitable for child under 1 year except in cases of failure to thrive

Resource® Thickened Drink (Nestlé)

Liquid, carbohydrate 22 g, energy: orange 382 kJ (90 kcal); apple 376 kJ (89 kcal)/100 mL. Flavours: apple or orange, syrup or custard consistencies. Gluten- and lactose-free, net price 12 × 114-mL cups = £7.44

For dysphagia. Not suitable for children under 1 year

Resource® ThickenUp® (Nestlé)

Powder, modified maize starch. Gluten- and lactose-free, net price 227 g = £4.55; 74 × 4.5-g sachet = £17.44

For thickening of foods in dysphagia. Not suitable for children under 1 year

Resource® ThickenUp® Clear (Nestlé)

Powder, maltodextrin, xanthan gum, gluten- and lactose-free, net price 125 g = £8.46; 24 × 1.2-g sachets = £5.28

For thickening of liquids or foods in dysphagia. Not suitable for children under 3 years

SLO Drinks® (SLO Drinks)

Powder, carbohydrate content varies with flavour and chosen consistency (3 consistencies available), see product literature. Flavours: black currant, lemon, orange; (hot drinks) chocolate, white coffee, white tea, net price 25 × 115 mL = £7.50

Nutritional supplement for patient hydration in the dietary management of dysphagia. Not suitable for children under 3 years

Thick and Easy® (Fresenius Kabi)

Powder. Modified maize starch, net price 225-g can = £4.93; 100 × 9-g sachets = £30.00; 4.54 kg = £82.56

For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive

Thicken Aid® (M & A Pharmachem)

Powder, modified maize starch, maltodextrin, gluten- and lactose-free, net price 225 g = £3.71; 100 × 9-g sachets = £22.40

For thickening of foods in dysphagia. Not suitable for children under 1 year

Thixo-D® (Sutherland)

Powder, modified maize starch, gluten-free. Net price 375-g tub = £7.15

For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive

Vitaquick® (Vitafo)

Powder. Modified maize starch. Net price 300 g = £6.87; 2 kg = £37.93; 6 kg = £98.22

For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive

A2.5.3 Flavouring preparations

Flavour Mix® (Nestlé)

Powder, flavours: banana, chocolate, coffee, lemon-lime, or strawberry, net price 60 g = £7.17

FlavourPac® (Vitafo)

Powder, flavours: black currant, lemon, orange, tropical or raspberry, net price 30 × 4-g sachets = £13.29

For use with Vitafo's range of unflavoured protein substitutes for metabolic diseases; not suitable for child under 1 year

Modjul® Flavour System (SHS)

Powder, carbohydrate-based flavours, black currant, orange, pineapple, 100 g = £11.60; cherry-vanilla, grapefruit, lemon-lime, 20 × 5-g sachets = £11.60

For use with unflavoured SHS products based on peptides or amino acids; not suitable for child under 6 months

A2.6 Foods for special diets

A2.6.1 Gluten-free foods

ACBS indications: established gluten-sensitive enteropathies including steatorrhoea due to gluten sensitivity, coeliac disease, and dermatitis herpetiformis.

Bread

Loaves

Barkat® (Gluten Free Foods Ltd)

Gluten-free. Loaf, multigrain 500 g = £5.73. Loaf, sliced, wholemeal 500 g = £3.98. Loaf, sliced, part-baked, country-style 250 g = £4.35. Loaf, sliced, part-baked, white 300 g = £4.13, 550 g = £5.78. Rice bread, brown 500 g = £5.73; 500 g = £5.73

Dietary Specials® (Nutrition Point)

Gluten-free. Loaf, sliced, multigrain, brown 400 g = £3.24; white 400 g = £3.24

Ener-G® (General Dietary)

Gluten-free. Loaf, sliced Seattle brown 600 g = £6.04. Rice bread, sliced, brown 474 g = £5.25; white 456 g = £5.25. Rice loaf, sliced 612 g = £5.25. Tapioca bread, sliced 480 g = £5.25

Genius Gluten Free® (Genius Foods)

Gluten-free. Loaf, unsliced, brown 400 g = £2.59; white 400 g = £2.59. Loaf, sliced, brown 400 g = £2.69; white 400 g = £2.69. Sandwich bread, sliced, brown 535 g = £3.48; white 535 g = £3.48

Glutafin® (Nutrition Point)

Gluten-free. Loaf, sliced, fibre 400 g = £3.77; white 400 g = £3.77

Glutafin® Select (Nutrition Point)

Gluten-free. Loaf, sliced, fresh, brown 400 g = £3.43; white 400 g = £3.43. Loaf, sliced, fibre 400 g = £3.36; white 400 g = £3.36. Loaf, seeded 400 g = £3.65

Juvela® (Juvela)

Gluten-free. Loaf, sliced, fresh, fibre 400 g = £3.39; white 400 g = £3.69. Loaf, sliced, white 400 g = £3.59; fibre 400 g = £3.54. Loaf, white 400 g = £3.54; fibre 400 g = £3.54. Loaf, part-baked, fibre 400 g = £3.80; white 400 g = £3.95

Lifestyle® (Ultraparm)

Gluten-free. Loaf, sliced, brown 400 g = £2.82; high fibre 400 g = £2.82; white 400 g = £2.82. Loaf, brown 400 g = £2.82; high fibre 400 g = £2.82; white 400 g = £2.82

Livwell® (Livwell)

Gluten-free. Loaf, sliced, brown (seeded) 200 g = £2.25; white 200 g = £2.25

Proceli® (Proceli)

Gluten-free. Loaf, sliced, white 165 g = £2.30; sandwich 155 g = £2.32. Rice bread, brown 220 g = £3.71; sandwich 220 g = £2.30

Ultra® (Ultraparm)

Gluten-free. Loaf, white 400 g = £2.82; high fibre 500 g = £3.35

Warburtons® (Warburtons)

Gluten-free. Loaf, sliced, brown 400 g = £2.99; white 400 g = £2.99

Wellfoods® (Wellfoods)

Gluten-free. Loaf, sliced 600 g = £4.95; unsliced 600 g = £4.85

Baguettes, buns and rolls

Barkat® (Gluten Free Foods Ltd)

Gluten-free. Baguette, part-baked 200 g = £4.35. Rolls, part-baked 2 × 100 g = £3.98; 6 × 50 g = £4.35

Ener-G® (General Dietary)

Gluten-free. Rolls, dinner × 6 = £3.56; white, long 4 × 55 g = £2.86; round 4 × 55 g = £2.86

Glutafin® (Nutrition Point)

Gluten-free. Baguette 2 × 175 g = £3.44. Rolls, fibre 4 × 50 g = £3.61; white 4 × 50 g = £3.61

Glutafin® Select (Nutrition Point)

Gluten-free. Rolls, part-baked, white 4 × 50 g = £3.61; long 2 × 75 g = £2.76

Juvela® (Juvela)

Gluten-free. Rolls, fresh, fibre 5 × 85 g = £4.42; white 5 × 85 g = £4.42. Rolls, fibre 5 × 85 g = £4.77; white 5 × 85 g = £4.77. Rolls, part-baked, fibre 5 × 75 g = £4.94; white 5 × 75 g = £4.94

Lifestyle® (Ultraparm)

Gluten-free. Rolls, brown 5 × 80 g = £2.82; high fibre 5 × 80 g = £2.82; white 5 × 80 g = £2.82

Livwell® (Livwell)

Gluten-free. Baguette, white 140 g = £2.15. Buns, toasting 4 × 45 g = £2.40. Rolls, white 4 = £2.25. Rolls, part-baked, circle (bagel) 2 × 70 g = £2.30; dinner (square) 2 × 80 g = £2.09

Proceli® (Proceli)

Gluten-free. Baguette, part-baked 2 × 125 g = £3.24. Buns 4 × 50 g = £3.41. Lunch rolls, white 8 × 34 g = £3.26. Rolls, hotdog 3 × 35 g = £2.24

Warburtons® (Warburtons)

Gluten-free. Baguette, 2 × 75 g = £2.79. Rolls, brown 3 × 100 g = £2.49; white 3 × 100 g = £2.49

Wellfoods® (Wellfoods)

Gluten-free. Burger buns 4 × 75 g = £3.95. Rolls 4 × 70 g = £3.65

Specialty breads

Livwell® (Livwell)

Gluten-free. Flat bread (pitta) 4 = £3.00. Tear-drop shape (naan) 2 × 90 g = £3.00

Cereals

Juvela® (Juvela)

Gluten-free. Fibre flakes 300 g = £2.78; flakes 300 g = £2.78; pure oats 500 g = £2.78

Nairns® (Nairns)

Gluten-free. Oat porridge 500 g = £2.89

Cookies and biscuits

Barkat® (Gluten Free Foods Ltd)

Gluten-free. Biscuits, coffee-style 200 g = £ 3.38; digestive 175 g = £2.61

Ener-G® (General Dietary)

Gluten-free. Cookies, vanilla 435 g = £5.98

Glutafin® (Nutrition Point)

Gluten-free. Biscuits, plain 200 g = £4.06; digestive 150 g = £2.09; savoury shorts 150 g = £2.75; shortbread 100 g = £1.69; sweet (without chocolate or sultanas) 150 g = £2.09; tea 150 g = £2.05

Juvela® (Juvela)

Gluten-free. Biscuits, digestive 150 g = £3.05; savoury 150 g = £3.82; sweet 150 g = £2.88, tea 150 g = £3.05

Crackers, crispbreads, and breadsticks

Barkat® (Gluten Free Foods Ltd)

Gluten-free. Crackers, round (matzo) 200 g = £3.52

Dietary Specials® (Nutrition Point)

Gluten-free. Cracker bread 150 g = £2.09

Glutafin® (Nutrition Point)

Gluten-free. Crackers, high fibre 200 g = £2.84; plain 200 g = £3.39; mini 175 g = £2.90

Juvela® (Juvela)

Gluten-free. Crispbread, plain 200 g = £4.64

Ultra® (Ultraparm)

Gluten-free. Crackerbread 200 g = £1.77

Warburtons® (Warburtons)

Gluten-free. Crackers, bran 150 g = £2.29

Flour mixes and xanthan gum

Flour mixes

Barkat® (Gluten Free Foods Ltd)

Gluten-free. Flour mix, bread 500 g = £6.81. Plain 750 g = £6.98

Finax® (Drossa)

Gluten-free. Flour mix, bread, fibre 1 kg = £9.92. Flour mix 900 g = £8.66; coarse 900 g = £8.66

Glutafin® (Nutrition Point)

Gluten-free. Flour mix, fibre 500 g = £6.53; white 500 g = £6.53

Glutafin Select® (Nutrition Point)

Gluten-free. Flour mix, bread, fibre 500 g = £6.53; white 500 g = £6.53. Fibre 500 g = £6.53; white 500 g = £6.53

Heron Foods® (Gluten Free Foods Ltd)

Gluten-free. Flour mix, organic, bread, standard 500 g = £8.96; high fibre 500 g = £8.96

Juvela® (Juvela)

Gluten-free. Flour mix, fibre 500 g = £7.35; plain 500 g = £7.35; harvest 500 g = £7.35

Mrs Crimbles® (Stiletto Foods)

Gluten-free. Bread mix, net price 275 g = £1.04. Pastry mix, net price 200 g = £1.04

Organi® (Community)

Gluten-free. Flour mix, bread 450 g = £3.10. Self-raising 500 g = £3.10. Pastry and pizza 375 g = £3.80

Procelli® (Proceli)

Gluten-free. Flour mix, white 1 kg = £9.95

Pure® (Innovative)

Gluten-free. Flour mix, blended 1 kg = £4.23. Potato starch 500 g = £1.68. Rice, brown 500 g = £1.58; white 500 g = £1.68. Tapioca starch 500 g = £2.26. Teff, brown 1 kg = £4.77; white 1 kg = £4.77

Tobia® (Tobia Teff)

Gluten-free. Flour mix, teff, brown 1 kg = £3.30; white 1 kg = £3.30

Tritamyl® (Gluten Free Foods Ltd)

Gluten-free. Flour mix, bread, brown 1 kg = £7.10; white 2 kg = £14.26. Plain 2 kg = £14.26

Wellfoods® (Wellfoods)

Gluten-free. Flour mix, plain 1 kg = £7.65

Xanthan gum

Ener-G® (General Dietary)

Gluten-free. Xanthan gum 170 g = £8.28

Pure® (Innovative)

Gluten-free. Xanthan gum 100 g = £6.66

Pasta

Barkat® (Gluten Free Foods Ltd)

Gluten-free. Pasta, animal shapes 500 g = £5.88; macaroni 500 g = £5.88; spaghetti 500 g = £5.88; spirals 500 g = £5.88; tagliatelle 500 g = £5.88. Buckwheat, penne 250 g = £2.93; spirals 250 g = £2.93

BiAlimenta® (Drossa)

Gluten-free. Pasta, acini di pepe 500 g = £5.97; formati misti 500 g = £5.97; penne 500 g = £5.97; sagnette 500 g = £5.97; spirali 500 g = £5.97; tubetti 500 g = £5.90; potato-based, gnocchi 500 g = £5.59; perle di gnocchi 500 g = £5.60

Dietary Specials® (Nutrition Point)

Gluten-free. Pasta, fusilli 500 g = £3.44; penne 500 g = £3.44; spaghetti 500 g = £3.44

Ener-G® (General Dietary)

Gluten-free. Pasta, rice-based, lasagne 454 g = £4.88; macaroni 454 g = £4.88; shells, small 454 g = £4.88 spaghetti 454 g = £4.88; vermicelli 300 g = £4.88

Glutafin® (Nutrition Point)

Gluten-free. Pasta, lasagne 250 g = £3.46; macaroni penne 500 g = £6.60; shells 500 g = £6.60; spirals 500 g = £6.60; spaghetti, long 500 g = £6.60; tagliatelle 250 g = £3.46

Juvela® (Juvela)

Gluten-free. Pasta, fusilli 500 g = £7.21; lasagne 250 g = £3.68; macaroni 500 g = £7.21; spaghetti 500 g = £7.21; tagliatelle 250 g = £3.47. Fibre, penne 500 g = £6.61

Orgran® (Community)

Gluten-free. Pasta, rice and corn, lasagne 200 g = £3.13; macaroni 250 g = £2.42. Spirals, buckwheat 250 g = £2.42; corn 250 g = £2.42; brown rice 250 g = £2.42; rice and corn 250 g = £2.42; rice and millet 250 g = £2.42

Proceli® (Proceli)

Gluten-free. Pasta, macaroni penne 250 g = £2.95; spirals 250 g = £2.59

Rizopia® (PGR Health Foods)

Gluten-free. Pasta, brown rice, fusilli 500 g = £2.72; lasagne 375 g = £2.72; penne 500 g = £2.72; spaghetti 500 g = £2.72

Ultra® (Ultraparm)

Gluten-free. Pasta, fusilli 250 g = £2.95; penne 250 g = £2.95; spaghetti 250 g = £2.95

Pizza bases**Barkat®** (Gluten Free Foods Ltd)

Gluten-free. Pizza crust, rice, brown 150 g = £5.00; white 150 g = £5.00

Dietary Specials® (Nutrition Point)

Gluten-free. Pizza base 2 × 150 g = £5.68

Glutafin® (Nutrition Point)

Gluten-free. Pizza base 2 × 150 g = £6.43

Juvela® (Juvela)

Gluten-free. Pizza base 2 × 180 g = £8.78

Proceli® (Proceli)

Gluten-free. Pizza base 2 × 250 g = £3.90

Ultra® (Ultraparm)

Gluten-free. Pizza base 2 × 200 g = £2.65

Wellfoods® (Wellfoods)

Gluten-free. Pizza base 2 × 300 g = £8.95

A2.6.1.1 Gluten- and wheat-free foods

ACBS indications: established gluten-sensitive enteropathies with coexisting established wheat sensitivity only.

Ener-G® (General Dietary)

Gluten-free, wheat-free. Bread loaf, six flour 576 g = £4.41. Rolls, Seattle brown, round (hamburger) 4 × 119 g = £3.96; long (hot dog) 4 × 119 g = £3.96. Pizza base, 3 × 124 g = £4.60

Glutafin® (Nutrition Point)

Gluten-free, wheat-free. Flour mix, bread 500 g = £6.53; fibre 500 g = £6.53. Crispbread 150 g = £3.19

Heron Foods® (Gluten Free Foods Ltd)

Gluten-free, wheat-free. Flour mix, organic, bread, fibre 500 g = £8.96. Bread and cake mix 500 g = £8.96

A2.6.2 Low-protein foods

ACBS indications: inherited metabolic disorders, renal or liver failure, requiring a low-protein diet

Bread**Ener-G®** (General Dietary)

Low protein. Rice bread, 600 g = £5.38

Juvela® (Juvela)

Low protein. Loaf, sliced 400 g = £3.64. Rolls 5 × 70 g = £4.52

Loprofin® (SHS)

Low protein. Loaf, part-baked, sliced 400 g = £3.80. Rolls, part-baked 4 × 65 g = £4.00

PK Foods® (Gluten Free Foods Ltd)

Low protein. Loaf, white, sliced 550 g = £4.75

Cake, biscuits, and snacks**Harifen®** (Ultraparm)

Low protein. Cracker toast, 200 g = £2.75

Juvela® (Juvela)

Low-protein. Cookies, cinnamon 125 g = £7.62; chocolate chip 110 g = £7.62; orange 125 g = £7.62

Loprofin® (SHS)

Low-protein. Wafers, chocolate 100 g = £2.46; vanilla 100 g = £2.46. Crackers 150 g = £3.45, herb 150 g = £3.45

PK Foods® (Gluten Free Foods Ltd)

Low-protein. *Aminex®* biscuits 200 g = £5.04; cookies 150 g = £5.04. Cookies, chocolate chip 150 g = £5.04; cinnamon 150 g = £5.04; orange 150 g = £5.04. Rusks 200 g = £5.04. Crispbread 75 g = £2.42

Promin® (Firstplay Dietary)

Low-protein. Cooked and flavoured Pasta Snax, ready-salted 12 × 25 g = £9.84; salt and vinegar 12 × 25 g = £9.84; cheese and onion 12 × 25 g = £9.84; jalapeno 12 × 25 g = £9.84

Taranis® (Firstplay Dietary)

Low-protein. Cake bars, apricot 6 × 40 g = £5.91, lemon 6 × 40 g = £5.91, pear 6 × 40 g = £5.91

Vita Bite® (Vitaflo)

Low protein. Bar, protein 30 mg (less than 2.5 mg phenylalanine), carbohydrate 15.35 g, fat 8.4 g, energy 572 kJ (137 kcal)/25 g. Chocolate flavoured, 25 g = £1.02
Not recommended for any child under 1 year

Vitaflo Choices® (Vitaflo)

Low-protein. Mini crackers, 40 g = £0.82
Not suitable for child under 3 years

Cereals**Loprofin®** (SHS)

Low-protein. Breakfast cereal flakes, apple 375 g = £7.60; chocolate 375 g = £7.60; strawberry 375 g = £7.60. Cereal loops 375 g = £7.88

Promin® (Firstplay Dietary)

Low-protein. Hot breakfast (powder sachets), apple and cinnamon 6 × 57 g = £7.87, banana 6 × 57 g = £7.87, chocolate 6 × 57 g = £7.87; original 6 × 56 g = £7.87

Desserts

Loprofin® (SHS)

Low-protein. Powder, chocolate 150 g = £4.65; strawberry 150 g = £4.65; vanilla 150 g = £4.65

PK Foods® (Gluten Free Foods Ltd)

Low-protein. Jelly, orange 4 × 80 g = £8.03, cherry 4 × 80 g = £8.03

ACBS Indications

Promin® (Firstplay Dietary)

Low-protein. Dessert mix, caramel 6 × 36.5 g = £6.18; custard 6 × 36.5 g = £6.18; chocolate and banana 6 × 36.5 g = £6.18; strawberry and vanilla 6 × 36.5 g = £6.18. Rice pudding imitation, apple 4 × 69 g = £6.18; banana 4 × 69 g = £6.18; original 4 × 69 g = £6.18; strawberry 4 × 69 g = £6.18

Flour mixes and egg substitutes

Ener-G® (General Dietary)

Low-protein. Egg replacer 454 g = £4.96

Fate® (Fate)

Low protein. All purpose mix 500 g = £6.97. Cake mix, 2 × 250 g = £6.97; chocolate-flavour 2 × 250 g = £6.97

Juvela® (Juvela)

Low-protein. Mix 500 g = £7.79

Loprofin® (SHS)

Low-protein. Mix, plain 500 g = £8.03; chocolate 500 g = £8.50; lemon 500 g = £8.50. Egg replacer 2 × 250 g = £14.78. Egg-white replacer 100 g = £9.50

PK Foods® (Gluten Free Foods Ltd)

Low-protein. Flour mix 750 g = £10.71. Egg replacer 350 g = £5.04

ACBS Indications

Pasta

Loprofin® (SHS)

Low-protein. Pasta, animal shapes 500 g = £8.09; spirals 500 g = £8.41; lasagne 250 g = £4.09; macaroni elbows 250 g = £4.04; penne 500 g = £8.41; spaghetti 500 g = £8.41; tagliatelle 250 g = £4.04; vermicelli 250 g = £4.17. Rice, imitation 500 g = £8.16

Promin® (Firstplay Dietary)

Low-protein. Pasta, alphabet shapes 500 g = £6.80; lasagne sheets 200 g = £2.95; macaroni 500 g = £6.80; noodles, flat 500 g = £6.80; shells 500 g = £6.80; spaghetti, short-cut 500 g = £6.80; spirals 500 g = £6.80. Rice, imitation 500 g = £6.80. Tricolour pasta, alphabet shapes 500 g = £6.80; shells 500 g = £6.80; spirals 500 g = £6.80

Pizza bases

Juvela® (Juvela)

Low-protein. Pizza base 2 × 180 g = £8.61

Savoury meals and mixes

Promin® (Firstplay Dietary)

Low-protein. Burger mix 2 × 62 g = £6.18; lamb & mint 2 × 62 g = £6.18. Couscous 500 g = £6.80. Pasta elbows in cheese and broccoli sauce 4 × 66 g = £8.08. Pasta meal 500 g = £6.80. Pasta shells in tomato, pepper, and herb sauce 4 × 72 g = £8.08. Pasta spirals in Moroccan sauce 4 × 72 g = £8.08. Sausage mix, apple & sage 4 × 30 g = £6.95; original 4 × 30 g = £6.95; tomato & basil 4 × 30 g = £6.95. Mac pot, cheese 4 × 61 g = £18.60; tomato 4 × 61 g = £18.60. Potato pot, cabbage and bacon 4 × 50 g = £15.95; onion 4 × 50 g = £15.95; sausage 4 × 50 g = £15.95. Xpot, all day scramble 4 × 60 g = £20.36; beef and tomato 4 × 60 g = £20.36; chip shop curry 4 × 60 g = £20.36; rogan style curry 4 × 60 g = £20.36

Spreads

Taranis® (Firstplay Dietary)

Low-protein. Spread, hazelnut 230 g = £7.65

A2.7 Nutritional supplements for metabolic diseases

Glutaric aciduria (type 1)

GA1 Anamix® Infant (SHS)

Powder, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; *standard dilution* (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL. Unflavoured, net price 400 g = £37.07 (5-g measuring scoop provided). Nutritional supplement for the dietary management of proven glutaric aciduria (type 1) in children from birth to 3 years

GA Gel® (Vitafo)

Gel, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 10 g, carbohydrate 10.3 g, fat trace, energy 339 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements. Unflavoured (flavouring: see *FlavourPac*®, p. 807), net price 30 × 24-g sachets = £204.80. Nutritional supplement for dietary management of type 1 glutaric aciduria in children 6 months–10 years

¹XYLS, Low TRY, Maxamaid® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *Modjul*® Flavour System, p. 807), net price 500 g = £93.59. Nutritional supplement for dietary management of type 1 glutaric aciduria

1. Maxamaid products are generally intended for use in children 1–8 years

XLYS, TRY, Glutaridon® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except lysine and tryptophan) 79 g, carbohydrate 4 g, energy 1411 kJ (332 kcal)/100 g, Lactose-free. Unflavoured, (flavouring: see *Modjuil®* Flavour System, p. 807), net price 2 × 500 g = £312.84

Nutritional supplement for type 1 glutaric aciduria in children and adults; requires additional source of vitamins, minerals and trace elements

Glycogen storage disease**Corn flour and corn starch**

For glycogen storage disease

Glycosade® (Vitaflo)

Powder, protein 200 mg, carbohydrate (maize starch) 47.6 g, fat 100 mg, fibre less than 600 mg, energy 803 kJ (192 kcal)/60 g, net price 30 × 60-g sachets = £107.64

A nutritional supplement for use in the dietary management of glycogen storage disease and other metabolic conditions where a constant supply of glucose is essential. Not suitable for use in children under 2 years

Homocystinuria or hypermethioninaemia**HCU Anamix® Infant (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except methionine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; *standard dilution* (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL. Unflavoured, net price 400 g = £37.07 (5-g measuring scoop provided)

Nutritional supplement for the dietary management of proven vitamin B₆ non-responsive homocystinuria or hypermethioninaemia in children from birth to 3 years

HCU cooler® 15 (Vitaflo)

Liquid, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 7 g, fat 500 mg, energy 393 kJ (92 kcal)/25 g with vitamins, minerals, and trace elements. Orange or red flavour, net price 30 × 130-mL pouch = £277.20

A methionine-free protein substitute for use as a nutritional supplement in children over 3 years with homocystinuria

HCU Express® 15 (Vitaflo)

Powder, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 3.8 g, fat 30 mg, energy 315 kJ (75.3 kcal)/25 g with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *FlavourPac®*, p. 807), net price 30 × 25-g sachets = £318.03

A methionine-free protein substitute for use as a nutritional supplement in children over 8 years with homocystinuria

HCU Express® 20 (Vitaflo)

Powder, protein (essential and non-essential amino acids except methionine) 20 g, carbohydrate 4.7 g, fat 70 mg, energy 416 kJ (99 kcal)/34 g with vitamins, minerals, and trace elements. Unflavoured (flavouring: see *FlavourPac®*, p. 807), net price 30 × 34-g sachets = £410.89

A methionine-free protein substitute for use as a nutritional supplement in children over 8 years with homocystinuria

HCU gel® (Vitaflo)

Powder, protein (essential and non-essential amino acids except methionine) 10 g, carbohydrate 10.3 g, fat 20 mg, energy 339 kJ (81 kcal)/24 g with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *FlavourPac®*, p. 807), net price 30 × 24-g sachets = £204.75

A methionine-free protein substitute for use as a nutritional supplement for the dietary management of children 1–10 years with homocystinuria

HCU Lophlex® LQ 20 (Nutricia Clinical)

Liquid, protein equivalent (essential and non-essential amino acids except methionine) 20 g, carbohydrate 8.8 g, fat 440 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements. Juicy berries flavour, net price 125 mL = £15.29

Nutritional supplement for the dietary management of homocystinuria in children over 3 years

HCU LV® (SHS)

Powder, protein (essential and non-essential amino acids except methionine) 20 g, carbohydrate 2.5 g, fat 190 mg, energy 390 kJ (92 kcal)/27.8-g sachet, with vitamins, minerals, and trace elements. Unflavoured (flavouring: see *Modjuil®* Flavour System, p. 807), or tropical flavour (formulation varies slightly), net price 30 × 27.8-g sachets = £469.80

Nutritional supplement for the dietary management of hypermethioninaemia or vitamin B₆ non-responsive homocystinuria in children over 8 years

XMET Homidon® (SHS)

Powder, protein equivalent (essential and non-essential amino acids, except methionine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. Unflavoured, (flavouring: see *Modjuil®* Flavour System, p. 807), net price 500 g = £171.63

Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria in children

¹XMET Maxamaid® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except methionine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured (flavouring: see *Modjuil®* Flavour System, p. 807), net price 500 g = £93.59

Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria

1. Maxamaid products are generally intended for use in children 1–8 years

¹XMET Maxamum® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except methionine) 39 g, carbohydrate 34 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *Modjul®* Flavour System, p. 807), net price 500 g = £150.02

Nutritional supplement for the dietary management of hypomethioninaemia or homocystinuria

²XLEU Maxamaid® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except leucine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *Modjul®* Flavour System, p. 807), net price 500 g = £93.59

Nutritional supplement for the dietary management of isovaleric acidemia

Hyperlysinaemia**HYPER LYS Anamix® Infant (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except lysine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; *standard dilution* (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL. Unflavoured, net price 400 g = £37.07 (5-g measuring scoop provided)

Nutritional supplement for the dietary management of proven hyperlysinaemia in children from birth to 3 years

²XYLS Maxamaid® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except lysine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *Modjul®* Flavour System, p. 807), net price 500 g = £93.59

Nutritional supplement for the dietary management of hyperlysinaemia

Isovaleric acidemia**IVA Anamix® Infant (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except leucine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; *standard dilution* (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL. Unflavoured, net price 400 g = £37.07 (5-g measuring scoop provided)

Nutritional supplement for the dietary management of proven isovaleric acidemia or other proven disorders of leucine metabolism in children from birth to 3 years

XLEU Faladon® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except leucine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. Unflavoured, (flavouring: see *Modjul®* Flavour System, p. 807), net price 200 g = £70.91

Nutritional supplement for the dietary management of isovaleric acidemia in children

Maple syrup urine disease**MSUD Aid III® (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. Unflavoured, (flavouring: see *Modjul®* Flavour System, p. 807), net price 500 g = £177.29

Nutritional supplement for the dietary management of maple syrup urine disease and related conditions in children and adults where it is necessary to limit the intake of branched chain amino acids

MSUD Anamix® Infant (SHS)

Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; *standard dilution* (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL. Unflavoured, net price 400 g = £37.07 (5-g measuring scoop provided)

Nutritional supplement for the dietary management of proven maple syrup urine disease in children from birth to 3 years

MSUD Anamix® Junior (SHS)

Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 8.4 g, carbohydrate 11 g, fat 3.9 g, energy 474 kJ (113 kcal)/29-g sachet, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *Modjul®* Flavour System, p. 807), net price 30 × 29-g sachets = £198.00

Nutritional supplement for the dietary management of maple syrup urine disease in children 1–10 years

MSUD Anamix® Junior LQ (SHS)

Liquid, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free. Orange flavour, net price 125-mL carton = £8.59

Nutritional supplement for the dietary management of maple syrup urine disease in children 1–10 years

MSUD cooler® 15 (Vitafo)

Liquid, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 15 g, carbohydrate 7 g, fat 500 mg, energy 393 kJ (92 kcal)/130-mL pouch, with vitamins, minerals, and trace elements. Orange or red flavour, net price 30 × 130-mL = £277.20

Nutritional supplement for the dietary management of maple syrup urine disease in children over 3 years and adults

1. Maxamum products are generally intended for use in children over 8 years
2. Maxamaid products are generally intended for use in children 1–8 years

MSUD express[®] 15 (Vitafo)

Powder, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 15 g, carbohydrate 3.8 g, fat less than 100 mg, energy 315 kJ (75 kcal)/25 g, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *FlavourPac[®]*, p. 807), net price 30 × 25-g sachets = £318.03

Nutritional supplement for the dietary management of maple syrup urine disease in children over 8 years and adults

MSUD express[®] 20 (Vitafo)

Powder, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/34 g, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *FlavourPac[®]*, p. 807), net price 30 × 34-g sachets = £410.89

Nutritional supplement for the dietary management of maple syrup urine disease in children over 8 years and adults

MSUD Gel[®] (Vitafo)

Powder, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 10 g, carbohydrate 10.3 g, fat less than 100 mg, energy 339 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *FlavourPac[®]*, p. 807), net price 30 × 24-g sachets = £207.15

Nutritional supplement for the dietary management of maple syrup urine disease in children 1–10 years

MSUD Lophlex[®] LQ 20 (Nutricia Clinical)

Liquid, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 20 g, carbohydrate 8.8 g, fat less than 500 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements. Juicy berries flavour, net price 125 mL = £15.29

Nutritional supplement for the dietary management of maple syrup urine disease in children over 3 years

¹MSUD Maxamaid[®] (SHS)

Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *Modjul[®]* Flavour System, p. 807), net price 500 g = £93.59

Nutritional supplement for the dietary management of maple syrup urine disease

²MSUD Maxamum[®] (SHS)

Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 39 g, carbohydrate 34 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Orange flavour or unflavoured, (flavouring: see *Modjul[®]* Flavour System, p. 807), net price 500 g = £150.02

Nutritional supplement for the dietary management of maple syrup urine disease

1. Maxamaid products are generally intended for use in children 1–8 years

2. Maxamum products are generally intended for use in children over 8 years

Methylmalonic or propionic acidaemia**MMA/PA Anamix[®] Infant** (SHS)

Powder, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; *standard dilution* (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

Unflavoured, net price 400 g = £37.07 (5-g measuring scoop provided)

Nutritional supplement for the dietary management of proven methylmalonic acidaemia or propionic acidaemia in children from birth to 3 years

XMTVI Asadon[®] (SHS)

Powder, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. Unflavoured, (flavouring: see *Modjul[®]* Flavour System, p. 807), net price 200 g = £70.91

Nutritional supplement for the dietary management of methylmalonic acidaemia or propionic acidaemia in children and adults

¹XMTVI Maxamaid[®] (SHS)

Powder, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *Modjul[®]* Flavour System, p. 807), net price 500 g = £93.59

Nutritional supplement for the dietary management of methylmalonic acidaemia or propionic acidaemia

²XMTVI Maxamum[®] (SHS)

Powder, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 39 g, carbohydrate 34 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see *Modjul[®]* Flavour System, p. 807), net price 500 g = £150.02

Nutritional supplement for the dietary management of methylmalonic acidaemia or propionic acidaemia

Other inborn errors of metabolism**Cystine500[®]** (Vitafo)

Powder, cystine 500 mg, carbohydrate 3.3 g, fat nil, energy 63 kJ (15 kcal)/4 g, net price 30 × 4-g sachets = £52.03

Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth

DocOmega[®] (Vitafo)

Powder, protein (cows' milk, soya) 100 mg, carbohydrate 3.2 g, fat 500 mg (of which docosahexaenoic acid 200 mg), fibre nil, energy 74 kJ (18 kcal)/4 g, with minerals, net price 30 × 4-g sachets = £37.66

Nutritional supplement for the dietary management of inborn errors of metabolism for adults and children from birth

EAA® Supplement (VitaFlo)

Powder, protein equivalent (essential amino acids) 5 g, carbohydrate 4 g, fat nil, energy 151 kJ (36 kcal)/12.5 g, with vitamins, minerals, and trace elements. Tropical flavour, net price 50 × 12.5-g sachets = £196.32

Nutritional supplement for the dietary management of disorders of protein metabolism including urea cycle disorders in children over 3 years

Isoleucine50® (VitaFlo)

Powder, isoleucine 50 mg, carbohydrate 3.8 g, fat nil, energy 63 kJ (15 kcal)/4 g, net price 30 × 4-g sachets = £52.03

Nutritional supplement for use in the dietary management of inborn errors of amino acid metabolism in adults and children from birth

KeyOmega® (VitaFlo)

Powder, protein (cows' milk, soya) 170 mg, carbohydrate 2.8 g, fat 800 mg (of which arachidonic acid 200 mg, docosahexaenoic acid 100 mg), energy 80 kJ (19 kcal)/4 g, net price 30 × 4-g sachet = £38.50

Nutritional supplement for the dietary management of inborn errors of metabolism

Leucine100® (VitaFlo)

Powder, leucine 100 mg, carbohydrate 3.7 g, fat nil, energy 63 kJ (15 kcal)/4 g, net price 30 × 4-g sachets = £52.03

Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth

Low protein drink (Milupa)

Powder, protein (cows' milk) 4.5 g (phenylalanine 100 mg), carbohydrate 59.5 g, fat 29.9 g, fibre nil, energy 2194 kJ (528 kcal)/100 g, with vitamins, minerals, and trace elements. Contains lactose. Net price 400 g = £8.80 (5-g measuring scoop provided)

Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children over 1 year

Note Termed *Milupa® lp-drink* by manufacturer

Phenylalanine50® (VitaFlo)

Powder, phenylalanine 50 mg, carbohydrate 3.8 g, fat nil, energy 63 kJ (15 kcal)/4 g, net price 30 × 4-g sachets = £50.52

Nutritional supplement for use in the dietary management of inborn errors of metabolism in adults and children from birth

ProZero® (VitaFlo)

Liquid, carbohydrate 8.1 g (of which sugars 3.5 g), fat 3.8 g, energy 278 kJ (66 kcal)/100 mL. Contains lactose. Net price 18 × 250 mL = £22.50; 6 × 1 litre = £30.00

A protein-free nutritional supplement for the dietary management of inborn errors of metabolism in children over 6 months and adults

Tyrosine1000® (VitaFlo)

Powder, tyrosine 1 g, carbohydrate 2.9 g, fat nil, energy 63 kJ (15 kcal)/4-g sachet, net price 30 × 4-g sachets = £4.77

Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth

Valine50® (VitaFlo)

Powder, valine 50 mg, carbohydrate 3.8 g, fat nil, energy 63 kJ (15 kcal)/4 g, net price 30 × 4-g sachets = £52.03

Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth

Phenylketonuria**Add-Ins®** (SHS)

Powder, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate nil, fat 5.1 g, energy 359 kJ (86 kcal)/18.2-g sachet, with vitamins, minerals, and trace elements. Unflavoured, net price 60 × 18.2-g sachets = £357.60

Nutritional supplement for the dietary management of proven phenylketonuria in children over 4 years

Easiphen® (SHS)

Liquid, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 6.7 g, carbohydrate 5.1 g, fat 2 g, energy 275 kJ (65 kcal)/100 mL with vitamins, minerals, and trace elements. Flavours: forest berries, orange, or tropical fruit, net price 250-mL carton = £9.19

Nutritional supplement for the dietary management of proven phenylketonuria in children over 8 years

Lophlex® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 2.5 g, fat 60 mg, fibre 220 mg, energy 385 kJ (91 kcal)/27.8-g sachet, with vitamins, minerals, and trace elements. Flavours: berry, orange, or unflavoured, net price 30 × 27.8-g sachets = £276.00

Nutritional supplement for the dietary management of proven phenylketonuria in children over 8 years and adults including pregnant women

Loprofin® PKU Drink (SHS)

Liquid, protein (cows' milk) 400 mg (phenylalanine 10 mg), lactose 9.4 g, fat 2 g, energy 165 kJ (40 kcal)/100 mL. Net price 200-mL carton = 72p

Nutritional supplement for the dietary management of phenylketonuria in children over 1 year

Loprofin® Sno-Pro (SHS)

Liquid, protein (cows' milk) 220 mg (phenylalanine 12.5 mg), carbohydrate 8 g, fat 3.8 g, energy 273 kJ (65 kcal)/100 mL. Contains lactose. Net price 200 mL = £1.19

Nutritional supplement for the dietary management of phenylketonuria, chronic renal failure and other inborn errors of amino acid metabolism

Milupa PKU 2-prima® (Milupa)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 60 g, carbohydrate 10 g, fat nil, energy 1190 kJ (280 kcal)/100 g, with vitamins, minerals, and trace elements. Vanilla flavour, net price 500 g = £149.25

Nutritional supplement for the dietary management of phenylketonuria in children 1–8 years

Milupa PKU 2-secunda® (Milupa)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 70 g, carbohydrate 6.8 g, fat nil, energy 1306 kJ (307 kcal)/100 g, with vitamins, minerals, and trace elements. Vanilla flavour, net price 500 g = £174.12
Nutritional supplement for the dietary management of phenylketonuria in children 9–15 years

Milupa PKU 3-advanta® (Milupa)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 70 g, carbohydrate 4.7 g, fat nil, energy 1270 kJ (299 kcal)/100 g, with vitamins, minerals, and trace elements. Vanilla flavour, net price 500 g = £174.12
Nutritional supplement for the dietary management of phenylketonuria in children over 15 years

Phlexy-10® Exchange System (SHS)

Capsules, protein equivalent (essential and non-essential amino acids except phenylalanine) 416.5 mg/capsule, net price 200-cap pack = £40.55

Tablets, protein equivalent (essential and non-essential amino acids except phenylalanine) 833 mg tablet, net price 75-tab pack = £26.26

Drink Mix, powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.33 g, carbohydrate 8.8 g/20-g sachet. Apple-black currant, citrus, or tropical flavour, net price 30 × 20-g sachet = £122.40

Nutritional supplement for the dietary management of phenylketonuria

Phlexy-Vits® (SHS)

Powder, vitamins, minerals, and trace elements, net price 30 × 7-g sachets = £68.10

Tablets, vitamins, minerals, and trace elements, net price 180-tab pack = £77.35

For use as a vitamin and mineral component of restricted therapeutic diets in children over 11 years and adults with phenylketonuria and similar amino acid abnormalities

PK Aid 4® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 79 g, carbohydrate 4.5 g, fat nil, energy 1420 kJ (334 kcal)/100 g. Unflavoured, (flavouring: see *Modju!*® Flavour System, p. 807), net price 500 g = £136.28 (5-g measuring scoop provided)
Nutritional supplement for the dietary management of phenylketonuria in children and adults

PKU Anamix® First Spoon (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 5 g, carbohydrate 4.8 g, fat 150 mg, fibre nil, energy 168 kJ (41 kcal)/12.5-g sachet, with vitamins, minerals, and trace elements, net price 30 × 12.5 g = £87.30

Nutritional supplement for the dietary management of proven phenylketonuria in children from 6 months to 5 years

PKU Anamix® Infant (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; *standard dilution* (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL. Unflavoured, net price 400 g = £33.69 (5-g measuring scoop provided)

Nutritional supplement for the dietary management of proven phenylketonuria in children from birth to 3 years

PKU Anamix® Junior (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.4 g, carbohydrate 9.9 g, fat 3.9 g, energy 455 kJ (108 kcal)/29-g sachet, with vitamins, minerals, and trace elements. Flavours: chocolate, pineapple-vanilla, or unflavoured (carbohydrate 11 g, energy 474 kJ (113 kcal)/29-g sachet), net price 30 × 29-g sachets = £120.30

Nutritional supplement for the dietary management of phenylketonuria in children 1–10 years

PKU Anamix Junior LQ® (SHS)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free. Flavours: Berry, orange, or unflavoured, net price 125-mL carton = £5.35

Nutritional supplement for the dietary management of phenylketonuria in children 1–10 years

PKU cooler10® (VitaFlo)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 5.1 g, energy 258 kJ (62 kcal)/87-mL pouch, with vitamins, minerals, and trace elements. Unflavoured (white) or flavoured (orange, purple, or red), net price 30 × 87-mL = £112.80

Nutritional supplement for the dietary management of phenylketonuria in children over 3 years

PKU cooler15® (VitaFlo)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 7.8 g, energy 386 kJ (92 kcal)/130-mL pouch, with vitamins, minerals, and trace elements. Unflavoured (white) or flavoured (orange, purple, or red), net price 30 × 130 mL = £168.00

Nutritional supplement for the dietary management of phenylketonuria in children over 3 years

PKU cooler20® (VitaFlo)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 10.2 g, energy 517 kJ (124 kcal)/174-mL pouch, with vitamins, minerals, and trace elements. Unflavoured (white) or flavoured (orange, purple, or red), net price 30 × 174 mL = £225.60
Nutritional supplement for the dietary management of phenylketonuria in children over 3 years

PKU express15® (Vitafo)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 2.4 g, energy 293 kJ (70 kcal)/25 g, with vitamins, minerals, and trace elements. Lemon, orange, tropical, or unflavoured (carbohydrate 3.4 g, energy 310 kJ (74 kcal)/25 g), (flavouring: see *FlavourPac*®, p. 807), net price 30 × 25-g sachets = £192.81

Nutritional supplement for the dietary management of phenylketonuria in children over 3 years

PKU express20® (Vitafo)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 3.3 g, energy 389 kJ (93 kcal)/34 g, with vitamins, minerals, and trace elements. Lemon, orange, tropical, or unflavoured (carbohydrate 4.7 g, energy 416 kJ (99 kcal)/34 g), (flavouring: see *FlavourPac*®, p. 807), net price 30 × 34-g sachets = £249.10

Nutritional supplement for the dietary management of phenylketonuria in children over 3 years

PKU gel® (Vitafo)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 8.9 g, fat less than 100 mg, energy 318 kJ (76 kcal)/24 g, with vitamins, minerals, and trace elements. Orange, raspberry, or unflavoured (carbohydrate 10.3 g, energy 339 kJ (81 kcal)/24 g), (flavouring: see *FlavourPac*®, p. 807), net price 30 × 24-g sachets = £133.39

For use as part of the low-protein dietary management of phenylketonuria in children 1–10 years

PKU Lophlex® LQ 10 (SHS)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 4.4 g, fibre 250 mg, energy 245 kJ (58 kcal)/62.5 mL, with vitamins, minerals, and trace elements. Flavours: berry, citrus, orange, or tropical, net price 62.5-mL carton = £4.93; juicy berries, juicy orange (energy 246 kJ (58 kcal)/62.5 mL), 62.5-mL carton = £4.93

Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women

PKU Lophlex® LQ 20 (SHS)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 8.8 g, fibre 340 mg, energy 490 kJ (115 kcal)/125 mL, with vitamins, minerals, and trace elements. Flavours: berry, citrus, orange, or tropical, net price 125-mL carton = £9.84; juicy berries, juicy orange (fibre 500 mg, energy 493 kJ (116 kcal)/125 mL), 125-mL carton = £9.84

Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women

PKU Lophlex® Sensation 20 (SHS)

Semi-solid, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 20.2 g, fibre 1 g, energy 706 kJ (166 kcal)/109 g, with vitamins, minerals, and trace elements. Flavours: berry or orange, net price 3 × 109-g pot = £31.44

Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women

PKU squeeze® (Vitafo)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 22.5 g, fat 500 mg, energy 565 kJ (135 kcal)/85 g, with vitamins, minerals, and trace elements. Flavour: apple-banana, net price 30 × 85-g pouch = £127.52

Nutritional supplement for the dietary management of phenylketonuria in children from 6 months to 10 years

PKU Start® (Vitafo)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 2 g, carbohydrate 8.3 g, fat 2.9 g, energy 286 kJ (68 kcal)/100 mL with vitamins, minerals, and trace elements. Contains lactose and fish oil. Net price 500-mL bottle = £6.53

For the dietary management of phenylketonuria in children under 12 months

L-Tyrosine (SHS)

Powder, L-tyrosine 20 g, carbohydrate 76.8 g, fat nil, energy 1612 kJ (379 kcal)/100 g, net price 100 g = £20.87

Nutritional supplement for the dietary management of phenylketonuria in pregnant women with low plasma tyrosine concentrations

¹XP Maxamaid® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Orange flavour, or unflavoured (flavouring: see *Modjul*® Flavour System, p. 807), net price 500 g = £55.37

Nutritional supplement for the dietary management of phenylketonuria in children 1–8 years

²XP Maxamum® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 39 g, carbohydrate 34 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Orange, or unflavoured (flavouring: see *Modjul*® Flavour System, p. 807), net price 30 × 50-g sachets = £256.80, 500 g = £85.63

Nutritional supplement for the dietary management of phenylketonuria in children over 8 years

Tyrosinaemia**Methionine-free TYR Anamix® Infant** (SHS)

Powder, protein equivalent (essential and non-essential amino acids except methionine, phenylalanine, and tyrosine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; *standard dilution* (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL. Unflavoured, net price 400 g = £37.07 (5-g measuring scoop provided)

Nutritional supplement for the dietary management of proven tyrosinaemia type 1 in children from birth to 3 years

1. Maxamaid products are generally intended for use in children 1–8 years
2. Maxamum products are generally intended for use in children over 8 years

TYR Anamix® Infant (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; *standard dilution* (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL. Unflavoured, net price 400 g = £37.07 (5-g measuring scoop provided). Nutritional supplement for the dietary management of proven tyrosinaemia where plasma-methionine concentrations are normal in children from birth to 3 years

TYR Anamix® Junior (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 8.4 g, carbohydrate 11 g, fat 3.9 g, energy 475 kJ (113 kcal)/29-g sachet, with vitamins, minerals, and trace elements. Unflavoured, net price 30 x 29-g sachets = £196.50. Nutritional supplement for the dietary management of proven tyrosinaemia in children 1–10 years

TYR Anamix® Junior LQ (SHS)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 500 kJ (119 kcal)/125 mL, with vitamins, minerals and trace elements. Orange flavour, net price 36 x 125-mL bottle = £272.79. Nutritional supplement for the dietary management of tyrosinaemia type I (when nitisinone (NTBC) is used, see section 9.8.1), type II, and type III, in children over 1 year

TYR cooler® 15 (VitaFlo)

Liquid, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 15 g, carbohydrate 7 g, fat 500 mg, energy 393 kJ (92 kcal)/130 mL, with vitamins, minerals, and trace elements. Orange or red flavour, net price 30 x 130-mL pouch = £277.20. Nutritional supplement for the dietary management of tyrosinaemia in children over 3 years

TYR express15® (VitaFlo)

Powder, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 15 g, carbohydrate 3.4 g, fat less than 100 mg, energy 310 kJ (74 kcal)/25 g, with vitamins, minerals, and trace elements. Unflavoured (flavouring: see *FlavourPac*®, p. 807), net price 30 x 25-g sachets = £318.03. Nutritional supplement for the dietary management of tyrosinaemia in children over 8 years

TYR express20® (VitaFlo)

Powder, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/34 g, with vitamins, minerals, and trace elements. Unflavoured (flavouring: see *FlavourPac*®, p. 807), net price 30 x 34-g sachets = £410.89. Nutritional supplement for the dietary management of tyrosinaemia in children over 8 years

TYR Gel® (VitaFlo)

Gel, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 10 g, carbohydrate 10.3 g, fat less than 100 mg, energy 339 kJ (81 kcal)/24 g, with vitamins, minerals and trace elements. Unflavoured (flavouring: see *FlavourPac*®, p. 807), net price 30 x 24-g sachets = £204.75. Nutritional supplement for the dietary management of tyrosinaemia in children 1–10 years

TYR Lophlex® LQ 20 (Nutricia Clinical)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 20 g, carbohydrate 8.8 g, fat less than 500 mg, fibre 500 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements. Juicy berries flavour, net price 125 mL = £15.29. Nutritional supplement for the dietary management of tyrosinaemia in children over 3 years

1XPHEN TYR Maxamaid® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured (flavouring: see *Modjul*® Flavour System, p. 807), net price 500 g = £93.59. Nutritional supplement for the dietary management of tyrosinaemia in children 1–8 years

XPHEN TYR Tyrosidon® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. Unflavoured (flavouring: see *Modjul*® Flavour System, p. 807), net price 500 g = £177.29. Nutritional supplement for the management of tyrosinaemia in children and adults where plasma-methionine concentrations are normal

XPTM Tyrosidon® (SHS)

Powder, protein equivalent (essential and non-essential amino acids except methionine, phenylalanine, and tyrosine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. Unflavoured (flavouring: see *Modjul*® Flavour System, p. 807), net price 500 g = £85.82. Nutritional supplement for the dietary management of tyrosinaemia type I in children and adults where plasma-methionine concentrations are above normal

Conditions for which ACBS products can be prescribed

Note This is a list of clinical conditions for which the ACBS has approved toilet preparations. For details of the preparations see Chapter 13.

Birthmarks

See Disfiguring skin lesions, below

Dermatitis

Aveeno® Bath Oil; *Aveeno*® Cream; *Aveeno*® lotion; *E45*® Emollient Bath Oil; *E45*® Emollient Wash Cream; *E45*® Lotion

Dermatitis herpetiformis

See also Gluten-sensitive enteropathies, p. 808

1. Maxamaid products are generally intended for use in children 1–8 years

Disfiguring skin lesions (birthmarks, mutilating lesions, scars, vitiligo)

Covermark® classic foundation and finishing powder;
Dermablend® Ultra corrective foundation;
Dermacolor® Camouflage cream and fixing powder;
Keromask® masking cream and finishing powder;
Veil® Cover cream and Finishing Powder. (Cleansing Creams, Cleansing Milks, and Cleansing Lotions are excluded)

Disinfectants (antiseptics)

May be prescribed on an FP10 only when ordered in such quantities and with such directions as are appropriate for the treatment of patients, but not for general hygienic purposes

Dry mouth (xerostomia)

For patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome.

AS Saliva Orthana®, *Biotène Oralbalance*®, *BioXtra*®, *Glandosane*®, *Saliveze*®

For details of preparations see section 12.3.5, p. 554

Eczema

See Dermatitis, above

Photodermatoses (skin protection in)

Anthelios® XL SPF 50+ Melt-in cream; *Sunsense*® Ultra; *Uvistat*® Lipscreen SPF 50, *Uvistat*® Suncream SPF 30 and 50

For details of preparations see section 13.8.1, p. 588

Pruritus

See Dermatitis, above

A3 Cautionary and advisory labels for dispensed medicines

Preparations in the *BNF for Children* include code numbers of the cautionary labels that pharmacists are recommended to add when dispensing. It is also expected that, when necessary, pharmacists will counsel children or their carers.

Counselling needs to be related to the age, experience, background, and understanding of the child or carer. The pharmacist should ensure understanding of how to take or use the medicine and how to follow the correct dosage schedule. Any effects of the medicine on co-ordination, performance of skilled tasks, any foods or medicines to be avoided, and what to do if a dose is missed should also be explained. Other matters, such as the possibility of staining of the clothes or skin, or discoloration of urine or stools by a medicine should also be mentioned.

For some preparations there is a special need for counselling, such as an unusual method or time of administration or a potential interaction with a common food or domestic remedy, and this should be mentioned where necessary.

Original packs Most preparations are now dispensed in unbroken original packs that include further advice for the patient in the form of patient information leaflets. The advice in patient information leaflets may be less appropriate when the medicine is for a child, particularly for unlicensed medicines or indications. Pharmacists should explain discrepancies to carers, if necessary. The patient information leaflet should only be withheld in exceptional circumstances because it contains other information that should be provided. Label 10 may be of value where appropriate. More general leaflets advising on the administration of preparations such as eye drops, eye ointments, inhalers, and suppositories are also available.

Scope of labels In general, no label recommendations are provided for injections on the assumption that they will be administered by a healthcare professional or a well-instructed child or carer. The labelling is not exhaustive and pharmacists are recommended to use their professional discretion in labelling new preparations and those for which no labels are shown.

Individual labelling advice is not given on the administration of the large variety of antacids. In the absence of instructions from the prescriber, and if on enquiry the patient has had no verbal instructions, the directions given under 'Dose' should be used on the label.

It is recognised that there may be occasions when pharmacists will use their knowledge and professional discretion and decide to omit one or more of the recommended labels for a particular child. In this case counselling is of the utmost importance. There may also be an occasion when a prescriber does not wish addi-

tional cautionary labels to be used, in which case the prescription should be endorsed 'NCL' (no cautionary labels). The exact wording that is required instead should then be specified on the prescription.

Pharmacists label medicines with various wordings in addition to those directions specified on the prescription. Such labels include 'Shake the bottle', 'For external use only', and 'Store in a cool place', as well as 'Discard . . . days after opening' and 'Do not use after . . .', which apply particularly to antibiotic mixtures, diluted liquid and topical preparations, and to eye-drops. Although not listed in the *BNF for Children* these labels should continue to be used when appropriate; indeed, 'For external use only' is a legal requirement on external liquid preparations, while 'Keep out of the reach of children' is a legal requirement on all dispensed medicines. Care should be taken not to obscure other relevant information with adhesive labelling.

It is the usual practice for patients to take standard tablets with water or other liquid and for this reason no separate label has been recommended.

The label wordings recommended by the *BNF for Children* apply to medicines dispensed against a prescription. Children and carers should be made aware that a dispensed medicine should never be taken by, or shared with, anyone other than for whom the prescriber intended it. Therefore, the *BNF for Children* does not include warnings against the use of a dispensed medicine by persons other than for whom it was specifically prescribed.

The label or labels for each preparation are recommended after careful consideration of the information available. However, it is recognised that in some cases this information may be either incomplete or open to a different interpretation. The *BNF for Children* will therefore be grateful to receive any constructive comments on the labelling suggested for any preparation.

Recommended label wordings

For *BNF for Children* 2011–2012, a revised set of cautionary and advisory labels has been introduced. All of the existing labels have been user-tested, and the revised wording selected reflects terminology that is better understood by patients.

Wordings which can be given as separate warnings are labels 1–19, 29–30, and 32. Wordings which can be incorporated in an appropriate position in the directions for dosage or administration are labels 21–28. A label has been omitted for number 20; labels 31 and 33 no longer apply to any medicines in the *BNF for children* and have therefore been deleted.

If separate labels are used it is recommended that the wordings be used without modification. If changes are made to suit computer requirements, care should be taken to retain the sense of the original.

- 1 **Warning: This medicine may make you sleepy**
To be used on *preparations for children* containing antihistamines, or other preparations given to children where the warnings of label 2 on driving or alcohol would not be appropriate.
- 2 **Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines. Do not drink alcohol**
To be used on *preparations for adults that can cause drowsiness*, thereby affecting the ability to drive and operate hazardous machinery; label 1 is more appropriate for children. *It is an offence to drive while under the influence of drink or drugs.*
Some of these preparations only cause drowsiness in the first few days of treatment and some only cause drowsiness in higher doses.
In such cases the patient should be told that the advice applies until the effects have worn off. However many of these preparations can produce a slowing of reaction time and a loss of mental concentration that can have the same effects as drowsiness.
Avoidance of alcoholic drink is recommended because the effects of CNS depressants are enhanced by alcohol. Strict prohibition however could lead to some patients not taking the medicine. Pharmacists should therefore explain the risk and encourage compliance, particularly in patients who may think they already tolerate the effects of alcohol (see also label 3). Queries from patients with epilepsy regarding fitness to drive should be referred back to the patient's doctor.
Side-effects unrelated to drowsiness that may affect a patient's ability to drive or operate machinery safely include *blurred vision, dizziness, or nausea*. In general, no label has been recommended to cover these cases, but the patient should be suitably counselled.
- 3 **Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines**
To be used on *preparations containing monoamine-oxidase inhibitors*; the warning to avoid alcohol and dealcoholised (low alcohol) drink is covered by the patient information leaflet.
Also to be used as for label 2 but where alcohol is not an issue.
- 4 **Warning: Do not drink alcohol**
To be used on *preparations where a reaction such as flushing may occur if alcohol is taken* (e.g. metronidazole). Alcohol may also enhance the hypoglycaemia produced by some oral antidiabetic drugs but routine application of a warning label is not considered necessary.
Patients should be advised not to drink alcohol for as long as they are receiving/using a course of medication, and in some cases for a period of time after the course is finished.
- 5 **Do not take indigestion remedies 2 hours before or after you take this medicine**
To be used with label 25 on *preparations coated to resist gastric acid* (e.g. enteric-coated tablets). This is to avoid the possibility of premature dissolution of the coating in the presence of an alkaline pH.
Label 5 also applies to drugs such as gabapentin *where the absorption is significantly affected by antacids*.
Pharmacists will be aware (from a knowledge of physiology) that the usual time during which indigestion remedies should be avoided is at least 2 hours before and after the majority of medicines have been taken; where a manufacturer advises a different time period, this can be followed, and should be explained to the patient.
- 6 **Do not take indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine**
To be used on *preparations containing ofloxacin and some other quinolones, doxycycline, lymecycline, minocycline, and penicillamine*. These drugs chelate calcium, iron, and zinc and are less well absorbed when taken with calcium-containing antacids or preparations containing iron or zinc. Pharmacists will be aware (from a knowledge of physiology) that these incompatible preparations should

be taken at least 2 hours apart for the majority of medicines; where a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

- 7 **Do not take milk, indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine**
To be used on *preparations containing ciprofloxacin, norfloxacin, or tetracyclines that chelate calcium, iron, magnesium, and zinc*, and are thus less available for absorption. Pharmacists will be aware (from a knowledge of physiology) that these incompatible preparations should be taken at least 2 hours apart for the majority of medicines; where a manufacturer advises a different time period, this can be followed, and should be explained to the patient. Doxycycline, lymecycline, and minocycline are less liable to form chelates and therefore only require label 6 (see above).
- 8 **Warning: Do not stop taking this medicine unless your doctor tells you to stop**
To be used on *preparations that contain a drug which is required to be taken over long periods without the patient necessarily perceiving any benefit* (e.g. antituberculous drugs).
Also to be used on *preparations that contain a drug whose withdrawal is likely to be a particular hazard* (e.g. clonidine for hypertension). Label 10 (see below) is more appropriate for corticosteroids.
- 9 **Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop**
To be used on *preparations where a course of treatment should be completed* to reduce the incidence of relapse or failure of treatment.
The preparations are antimicrobial drugs given by mouth. Very occasionally, some may have severe side-effects (e.g. diarrhoea in patients receiving clindamycin) and in such cases the patient may need to be advised of reasons for stopping treatment quickly and returning to the doctor.
- 10 **Warning: Read the additional information given with this medicine**
To be used particularly on *preparations containing anticoagulants, lithium, and oral corticosteroids*. The appropriate treatment card should be given to the patient and any necessary explanations given.
This label may also be used on other preparations to remind the patient of the instructions that have been given.
- 11 **Protect your skin from sunlight—even on a bright but cloudy day. Do not use sunbeds**
To be used on *preparations that may cause phototoxic or photoallergic reactions* if the patient is exposed to ultraviolet radiation. Many drugs other than those listed (e.g. phenothiazines and sulfonamides) may on rare occasions cause reactions in susceptible patients. Exposure to high intensity ultraviolet radiation from sunray lamps and sunbeds is particularly likely to cause reactions.
- 12 **Do not take anything containing aspirin while taking this medicine**
To be used on *preparations containing probenecid and sulfinpyrazone* whose activity is reduced by aspirin.
Label 12 should not be used for anticoagulants since label 10 is more appropriate.
- 13 **Dissolve or mix with water before taking**
To be used on *preparations that are intended to be dissolved in water* (e.g. soluble tablets) or *mixed with water* (e.g. powders, granules) before use. In a few cases other liquids such as fruit juice or milk may be used.
- 14 **This medicine may colour your urine. This is harmless**
To be used on *preparations that may cause the patient's urine to turn an unusual colour*. These include triamterene (blue under some lights), levodopa (dark reddish), and rifampicin (red).
- 15 **Caution: flammable. Keep your body away from fire or flames after you have put on the medicine**
To be used on *preparations containing sufficient flammable solvent to render them flammable if exposed to a naked flame*.

- 16 **Dissolve the tablet under your tongue—do not swallow. Store the tablets in this bottle with the cap tightly closed. Get a new supply 8 weeks after opening**
To be used on *glyceryl trinitrate* tablets to remind the patient not to transfer the tablets to plastic or less suitable containers.
- 17 **Do not take more than . . . in 24 hours**
To be used on *preparations for the treatment of acute migraine* except those containing ergotamine, for which label 18 is used. The dose form should be specified, e.g. tablets or capsules.
It may also be used on preparations for which no dose has been specified by the prescriber.
- 18 **Do not take more than . . . in 24 hours. Also, do not take more than . . . in any one week**
To be used on preparations containing ergotamine. The dose form should be specified, e.g. tablets or suppositories.
- 19 **Warning: This medicine makes you sleepy. If you still feel sleepy the next day, do not drive or use tools or machines. Do not drink alcohol**
To be used on *preparations containing hypnotics (or some other drugs with sedative effects) prescribed to be taken at night*. On the rare occasions (e.g. nitrazepam in epilepsy) when hypnotics are prescribed for daytime administration this label would clearly not be appropriate. Also to be used as an *alternative to the label 2 wording* (the choice being at the discretion of the pharmacist) *for anxiolytics prescribed to be taken at night*.
It is hoped that this wording will convey adequately the problem of residual morning sedation after taking 'sleeping tablets'.
- 21 **Take with or just after food, or a meal**
To be used on *preparations that are liable to cause gastric irritation, or those that are better absorbed with food*.
Patients should be advised that a *small amount of food is sufficient*.
- 22 **Take 30 to 60 minutes before food**
To be used on some preparations whose absorption is thereby improved.
Most oral antibacterials require label 23 instead (see below).
- 23 **Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food**
To be used on *oral antibacterials whose absorption may be reduced by the presence of food and acid in the stomach*.
- 24 **Suck or chew this medicine**
To be used on *preparations that should be sucked or chewed*.
The pharmacist should use discretion as to which of these words is appropriate.
- 25 **Swallow this medicine whole. Do not chew or crush**
To be used on *preparations that are enteric-coated or designed for modified-release*.
Also to be used on *preparations that taste very unpleasant or may damage the mouth* if not swallowed whole.
Patients should be advised (where relevant) that some modified-release preparations can be broken in half, but that the halved tablet should still be swallowed whole, and not chewed or crushed.
- 26 **Dissolve this medicine under your tongue**
To be used on *preparations designed for sublingual use*.
Patients should be advised to hold under the tongue and avoid swallowing until dissolved. The buccal mucosa between the gum and cheek is occasionally specified by the prescriber.
- 27 **Take with a full glass of water**
To be used on *preparations that should be well diluted* (e.g. chloral hydrate), *where a high fluid intake is required* (e.g. sulfonamides), or *where water is required to aid the action* (e.g. methylcellulose). The patient should be advised that 'a full glass' means at least 150 mL. In most cases fruit juice, tea, or coffee may be used.
- 28 **Spread thinly on the affected skin only**
To be used on *external preparations* that should be applied sparingly (e.g. corticosteroids, dithranol).
- 29 **Do not take more than 2 at any one time. Do not take more than 8 in 24 hours**
To be used on containers of dispensed *solid dose preparations containing paracetamol* for adults when the instruction on the label indicates that the dose can be taken on an 'as required' basis. The dose form should be specified, e.g. tablets or capsules.
This label has been introduced because of the serious consequences of overdosage with paracetamol.
- 30 **Contains paracetamol. Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine, even if you feel well**
To be used on all containers of dispensed *preparations containing paracetamol*.
- 32 **Contains aspirin. Do not take anything else containing aspirin while taking this medicine**
To be used on containers of dispensed *preparations containing aspirin when the name on the label does not include the word 'aspirin'*.

A4 Intravenous infusions for neonatal intensive care

Intravenous policy A local policy on the dilution of drugs with intravenous fluids should be drawn up by a multi-disciplinary team and issued as a document to the members of staff concerned.

Centralised additive services are provided in a number of hospital pharmacy departments and should be used in preference to making additions on wards.

The information that follows should be read in conjunction with local policy documents.

Guidelines

1. Drugs should only be diluted with infusion fluid when constant plasma concentrations are needed or when the administration of a more concentrated solution would be harmful.
2. In general, only one drug should be mixed with an infusion fluid in a syringe and the components should be compatible. Ready-prepared solutions should be used whenever possible. Drugs should not normally be added to blood products, mannitol, or sodium bicarbonate. Only specially formulated additives should be used with fat emulsions or amino-acid solutions (section 9.3).
3. Solutions should be thoroughly mixed by shaking and checked for absence of particulate matter before use.
4. Strict asepsis should be maintained throughout and in general the giving set should not be used for more than 24 hours (for drug admixtures).
5. The infusion syringe should be labelled with the neonate's name and hospital number, the name and quantity of drug, the infusion fluid, and the expiry date and time. If a problem occurs during administration, containers should be retained for a period after use in case they are needed for investigation.
6. Administration using a suitable motorised syringe driver is advocated for preparations where strict control over administration is required.
7. It is good practice to examine intravenous infusions from time to time while they are running. If cloudiness, crystallisation, change of colour, or any other sign of interaction or contamination is observed the infusion should be discontinued.

Problems

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

Incompatibility Physical and chemical incompatibilities may occur with loss of potency, increase in toxicity, or other adverse effect. The solutions may become opalescent or precipitation may occur, but in many instances there is no visual indication of incompatibility. Interaction may take place at any point in the infusion fluid pathway, and the potential for incompatibility is increased when more than one substance is added to the infusion fluid.

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

A number of preparations undergo significant loss of potency when added singly or in combination to large volume infusions. Examples include ampicillin in infusions that contain glucose or lactates.

Blood Because of the large number of incompatibilities, drugs should not be added to blood and blood products for infusion purposes. Examples of incompatibility with blood include hypertonic mannitol solutions (irreversible crenation of red cells), dextrans (rouleaux formation and interference with cross-matching), glucose (clumping of red cells), and oxytocin (inactivated).

If the giving set is not changed after the administration of blood, but used for other infusion fluids, a fibrin clot may form which, apart from blocking the set, increases the likelihood of microbial growth.

Intravenous fat emulsions These may break down with coalescence of fat globules and separation of phases when additions such as antibacterials or electrolytes are made, thus increasing the possibility of embolism. Only specially formulated products such as *Vitlipid N*[®] (section 9.3) may be added to appropriate intravenous fat emulsions.

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

Method

Ready-prepared infusions should be used whenever available. When dilution of drugs is required to be made extemporaneously, any product reconstitution

instructions such as those relating to concentration, vehicle, mixing, and handling precautions should be strictly followed using an aseptic technique throughout. Once the product has been reconstituted, further dilution with the infusion fluid should be made immediately in order to minimise microbial contamination and, with certain products, to prevent degradation or other formulation change which may occur; e.g. reconstituted ampicillin injection degrades rapidly on standing, and also may form polymers which could cause sensitivity reactions.

It is also important in certain instances that an infusion fluid of specific pH be used (e.g. **furosemide** injection requires dilution in infusions of pH greater than 5.5).

When drug dilutions are made it is important to mix thoroughly; additions should not be made to an infusion container that has been connected to a giving set, as mixing is hampered. If the solutions are not thoroughly mixed, a concentrated layer of the drug may form owing to differences in density. **Potassium chloride** is particularly prone to this 'layering' effect when added without adequate mixing to infusions; if such a mixture is administered it may have a serious effect on the heart.

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

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

Table of drugs given by continuous intravenous infusion to neonates

The table lists key drugs given by continuous intravenous infusion to neonates.

Covers dilution with *Glucose intravenous infusion* 5% and 10% and *Sodium chloride intravenous infusion* 0.9%. Compatibility with glucose 5% and with sodium chloride 0.9% indicates compatibility with *Sodium chloride and glucose intravenous infusion*. Infusion of a large volume of hypotonic solution should be avoided, therefore care should be taken if water for injections is used.

Adrenaline/Epinephrine (p. 112)

Dilute 3 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 100 nanograms/kg/minute; infuse through a central venous catheter. Incompatible with bicarbonate and alkaline solutions.

Note Usually made up with adrenaline 1 in 1000 (1 mg/mL) solution; this concentration of adrenaline is not licensed for intravenous administration

Alprostadil (*Prostin VR*®) (p. 130)

Dilute 150 micrograms/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 nanograms/kg/minute. Undiluted solution must not come into contact with the barrel of the plastic syringe; add the required volume of alprostadil to a volume of infusion fluid in the syringe, and then make up to final volume

Atracurium besilate (p. 648)

Dilute 60 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 120 micrograms/kg/hour; minimum concentration of 500 micrograms/mL, max. concentration of 5 mg/mL

Dobutamine (as hydrochloride) (p. 109)

Dilute 30 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.5 mL/hour provides a dose of 5 micrograms/kg/minute; max. concentration of 5 mg/mL; infuse higher concentration solutions through central venous catheter only. Incompatible with bicarbonate and other strong alkaline solutions

Dopamine hydrochloride (p. 110)

Dilute 30 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.3 mL/hour provides a dose of 3 micrograms/kg/minute; max. concentration of 3.2 mg/mL; infuse higher concentration solutions through central venous catheter. Incompatible with bicarbonate and other alkaline solutions

Epoprostenol (*Flolan*®) (p. 94)

Reconstitute the 500-microgram vial using the glycine buffer diluent provided to make a 10 micrograms/mL concentrate (pH 10.5); filter the concentrate using the filter provided; the concentrate can be administered via a central venous catheter, or it may be diluted further.

Neonate body-weight under 2 kg, using the concentrate, dilute 150 micrograms/kg body-weight to a final volume of 50 mL with Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 nanograms/kg/minute.

Neonate body-weight over 2 kg, using the concentrate, dilute 60 micrograms/kg body-weight to a final volume of 50 mL with Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 2 nanograms/kg/minute.

Note Diluted solution stable for 12 hours at room temperature, although some units use for 24 hours and allow for loss of potency. Minimum concentration of 1.43 micrograms/mL

Intravenous infusion information for neonatal intensive care *only*; for information in other children, see individual drug monographs.

Glyceryl trinitrate (p. 103)

Dilute 3 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 1 mL/hour provides a dose of 1 microgram/kg/minute; max. concentration of 400 micrograms/mL (but concentration of 1 mg/mL has been used via a central venous catheter).

Note Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used

Heparin (as sodium) (p. 113)

Maintenance of umbilical arterial catheter, dilute 50 units to a final volume of 50 mL with Sodium Chloride 0.45% or use ready-made bag containing 500 units in 500 mL Sodium Chloride 0.9%; infuse at 0.5 mL/hour.

Treatment of thrombosis, dilute 1250 units/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 1 mL/hour provides a dose of 25 units/kg/hour

Insulin (soluble) (p. 359)

Dilute 5 units to a final volume of 50 mL with Sodium Chloride 0.9% and mix thoroughly; an intravenous infusion rate of 0.1 mL/kg/hour provides a dose of 0.01 units/kg/hour.

Note Insulin may be absorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin

Midazolam (p. 238 and p. 643)

Dilute 15 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 30 micrograms/kg/hour

Intravenous infusion information for neonatal intensive care *only*; for information in other children, see individual drug monographs.

Morphine sulfate (p. 208)

Dilute 2.5 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or 10% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 micrograms/kg/hour

Noradrenaline/Norepinephrine (p. 111)

Dilute 600 micrograms (base)/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride and Glucose; an intravenous infusion rate of 0.1 mL/hour provides a dose of 20 nanograms (base)/kg/minute; infuse through central venous catheter; max. concentration of noradrenaline (base) 40 micrograms/mL (higher concentrations can be used if fluid restricted). Discard if discoloured.

Incompatible with bicarbonate or alkaline solutions.

Note 500 micrograms of noradrenaline base is equivalent to 1 mg of acid tartrate. Dose expressed as the base

Vecuronium (p. 650)

Reconstitute each vial with 5 mL Water for Injections to give a 2 mg/mL solution. Dilute 5 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.5 mL/hour provides a dose of 50 micrograms/kg/hour; minimum concentration of 40 micrograms/mL

Dental Practitioners' Formulary

List of Dental Preparations

The following list has been approved by the appropriate Secretaries of State, and the preparations therein may be prescribed by dental practitioners on form FP10D (GP14 in Scotland, WP10D in Wales).

Licensed **sugar-free** versions, where available, are preferred.

Licensed **alcohol-free** mouthwashes, where available, are preferred.

Aciclovir Cream, BP
Aciclovir Oral Suspension, BP, 200 mg/5 mL
Aciclovir Tablets, BP, 200 mg
Aciclovir Tablets, BP, 800 mg
Amoxicillin Capsules, BP
Amoxicillin Oral Powder, DPF
Amoxicillin Oral Suspension, BP
Artificial Saliva Gel, DPF
Artificial Saliva Oral Spray, DPF
Artificial Saliva Pastilles, DPF
Artificial Saliva Protective Spray, DPF

¹Artificial Saliva Substitutes as listed below (to be prescribed only for indications approved by ACBS):

AS Saliva Orthana®
Glandosane®
BioXtra® Gel Mouthspray
BioXtra® Moisturising Gel
Saliveze®

²Aspirin Tablets, Dispersible, BP
Azithromycin Capsules, 250 mg, DPF
Azithromycin Oral Suspension, 200 mg/5 mL, DPF
Azithromycin Tablets, 250 mg, DPF
Azithromycin Tablets, 500 mg, DPF
Beclomethasone Pressurised Inhalation, BP, 50 micrograms/metered inhalation, CFC-free, as:

Clenil Module®

Benzydamine Mouthwash, BP 0.15%
Benzydamine Oromucosal Spray, BP 0.15%
Betamethasone Soluble Tablets, 500 micrograms, DPF
Carbamazepine Tablets, BP
Cefalexin Capsules, BP
Cefalexin Oral Suspension, BP
Cefalexin Tablets, BP
Cefradine Capsules, BP
Cetirizine Oral Solution, BP, 5 mg/5 mL
Cetirizine Tablets, BP, 10 mg
Chlorhexidine Gluconate Gel, BP
Chlorhexidine Mouthwash, BP
Chlorhexidine Oral Spray, DPF
Chlorphenamine Oral Solution, BP
Chlorphenamine Tablets, BP
Choline Salicylate Dental Gel, BP
Clarithromycin Oral Suspension, 125 mg/5 mL, DPF
Clarithromycin Oral Suspension, 250 mg/5 mL, DPF
Clarithromycin Tablets, BP
Clindamycin Capsules, BP

Co-amoxiclav Tablets, BP, 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt)
Co-amoxiclav Oral Suspension, BP, 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31.25 mg as potassium salt)/5 mL
Co-amoxiclav Oral Suspension, BP, 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62.5 mg as potassium salt)/5 mL
Diazepam Oral Solution, BP, 2 mg/5 mL
Diazepam Tablets, BP
Diclofenac Sodium Tablets, Gastro-resistant, BP
Dihydrocodeine Tablets, BP, 30 mg
Doxycycline Tablets, Dispersible, BP
Doxycycline Capsules, BP, 100 mg
³Doxycycline Tablets, 20 mg, DPF
Ephedrine Nasal Drops, BP
Erythromycin Ethyl Succinate Oral Suspension, BP
Erythromycin Ethyl Succinate Tablets, BP
Erythromycin Stearate Tablets, BP
Erythromycin Tablets, Gastro-resistant, BP
Fluconazole Capsules, 50 mg, DPF
Fluconazole Oral Suspension, 50 mg/5 mL, DPF
Hydrocortisone Cream, BP, 1%
Hydrocortisone Oromucosal Tablets, BP
Hydrogen Peroxide Mouthwash, BP, 6%
Ibuprofen Oral Suspension, BP, sugar-free
Ibuprofen Tablets, BP
Lansoprazole Capsules, Gastro-resistant, BP
Lidocaine Ointment, BP, 5%
Lidocaine Spray 10%, DPF
Loratadine Syrup, 5 mg/5 mL, DPF
Loratadine Tablets, BP, 10 mg
⁴Menthol and Eucalyptus Inhalation, BP 1980
Metronidazole Oral Suspension, BP
Metronidazole Tablets, BP
Miconazole Cream, BP
Miconazole Oromucosal Gel, BP
Miconazole and Hydrocortisone Cream, BP
Miconazole and Hydrocortisone Ointment, BP
Nystatin Oral Suspension, BP
Omeprazole Capsules, Gastro-resistant, BP
Oxytetracycline Tablets, BP
⁵Paracetamol Oral Suspension, BP
Paracetamol Tablets, BP
Paracetamol Tablets, Soluble, BP
Penciclovir Cream, DPF
Phenoxymethylpenicillin Oral Solution, BP
Phenoxymethylpenicillin Tablets, BP
Promethazine Hydrochloride Tablets, BP
Promethazine Oral Solution, BP
Saliva Stimulating Tablets, DPF
Sodium Chloride Mouthwash, Compound, BP
Sodium Fluoride Mouthwash, BP
Sodium Fluoride Oral Drops, BP

1. Indications approved by the ACBS are: patients suffering from dry mouth as a result of having (or having undergone) radiotherapy or sicca syndrome
2. The BP directs that when soluble aspirin tablets are prescribed, dispersible aspirin tablets should be dispensed

3. May be difficult to obtain
4. This preparation does not appear in subsequent editions of the BP
5. The BP directs that when Paediatric Paracetamol Oral Suspension or Paediatric Paracetamol Mixture is prescribed and no strength stated Paracetamol Oral Suspension 120 mg/5 mL should be dispensed

Sodium Fluoride Tablets, BP
Sodium Fluoride Toothpaste 0.619%, DPF
Sodium Fluoride Toothpaste 1.1%, DPF
Sodium Fusidate Ointment, BP
Temazepam Oral Solution, BP
Temazepam Tablets, BP
Tetracycline Tablets, BP

Nurse Prescribers' Formulary

Nurse Prescribers' Formulary for Community Practitioners

Nurse Prescribers' Formulary Appendix (Appendix NPF). List of preparations approved by the Secretary of State which may be prescribed on form FP10P (form HS21(N) in Northern Ireland, form GP10(N) in Scotland, forms FP10(CN) and FP10(PN) in Wales or, when available, WP10CN and WP10PN in Wales) by Nurses for National Health Service patients.

Community practitioners who have completed the necessary training may only prescribe items appearing in the nurse prescribers' list set out below. Community Practitioner Nurse Prescribers are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved generic name.

Medicinal Preparations

Almond Oil Ear Drops, BP
 Arachis Oil Enema, NPF
¹Aspirin Tablets, Dispersible, 300 mg, BP
 Bisacodyl Suppositories, BP (includes 5-mg and 10-mg strengths)
 Bisacodyl Tablets, BP
 Catheter Maintenance Solution, Sodium Chloride, NPF
 Catheter Maintenance Solution, 'Solution G', NPF
 Catheter Maintenance Solution, 'Solution R', NPF
 Chlorhexidine Gluconate Alcoholic Solutions containing at least 0.05%
 Chlorhexidine Gluconate Aqueous Solutions containing at least 0.05%
 Choline Salicylate Dental Gel, BP
 Clotrimazole Cream 1%, BP
 Co-danthramer Capsules, NPF
 Co-danthramer Capsules, Strong, NPF
 Co-danthramer Oral Suspension, NPF
 Co-danthramer Oral Suspension, Strong, NPF
 Co-danthrusate Capsules, BP
 Co-danthrusate Oral Suspension, NPF
 Crotaamiton Cream, BP
 Crotaamiton Lotion, BP
 Dimeticone barrier creams containing at least 10%
 Dimeticone Lotion, NPF
 Docusate Capsules, BP
 Docusate Enema, NPF
 Docusate Oral Solution, BP
 Docusate Oral Solution, Paediatric, BP
 Econazole Cream 1%, BP
 Emollients as listed below:

Aquadrate® 10% w/w Cream
 Arachis Oil, BP
 Balneum® Plus Cream
 Cetaben® Emollient Cream
 Dermamist®
 Diprobace® Cream
 Diprobace® Ointment
 Doublebase®
 Doublebase® Dayleve Gel

E45® Cream
 E45® Itch Relief Cream
 Emulsifying Ointment, BP
 Eucerin® Intensive 10% w/w Urea Treatment Cream
 Eucerin® Intensive 10% w/w Urea Treatment Lotion
 Hydromol® Cream
 Hydromol® Intensive
 Hydrous Ointment, BP
 Lipobase®
 Liquid and White Soft Paraffin Ointment, NPF
 Neutrogena® Norwegian Formula Dermatological Cream
 Nutraplus® Cream
 Oilatum® Cream
 Oilatum® Junior Cream
 Paraffin, White Soft, BP
 Paraffin, Yellow Soft, BP
 Ultrabase®
 Unguentum M®

Emollient Bath and Shower Preparations as listed below:

Aqueous Cream, BP
²Balneum®
²Balneum Plus® Bath Oil
 Cetaben® Emollient Bath Additive
 Dermalmo® Bath Emollient
 Doublebase® Emollient Bath Additive
 Doublebase® Emollient Shower Gel
 Doublebase® Emollient Wash Gel
 Hydromol® Bath and Shower Emollient
 Oilatum® Emollient
 Oilatum® Gel
 Oilatum® Junior Bath Additive
 Zerolatum® Emollient Medicinal Bath Oil

Folic Acid Tablets 400 micrograms, BP
 Glycerol Suppositories, BP
³Ibuprofen Oral Suspension, BP
³Ibuprofen Tablets, BP
 Ispaghula Husk Granules, BP
 Ispaghula Husk Granules, Effervescent, BP
 Ispaghula Husk Oral Powder, BP
 Lactulose Solution, BP
 Lidocaine Ointment, BP
 Lidocaine and Chlorhexidine Gel, BP
 Macrogol Oral Liquid, Compound, NPF
 Macrogol Oral Powder, Compound, NPF
 Macrogol Oral Powder, Compound, Half-strength, NPF
 Magnesium Hydroxide Mixture, BP
 Magnesium Sulfate Paste, BP
 Malathion aqueous lotions containing at least 0.5%
 Mebendazole Oral Suspension, NPF
 Mebendazole Tablets, NPF
 Methylcellulose Tablets, BP
 Miconazole Cream 2%, BP
 Miconazole Oromucosal Gel, BP
 Mouthwash Solution-tablets, NPF

2. Except pack sizes that are not to be prescribed under the NHS (see Part XVIII of the Drug Tariff, Part XI of the Northern Ireland Drug Tariff)
3. Except for indications and doses that are (PoM)

Nicotine Inhalation Cartridge for Oromucosal Use, NPF
 Nicotine Lozenge, NPF
 Nicotine Medicated Chewing Gum, NPF
 Nicotine Nasal Spray, NPF
 Nicotine Oral Spray, NPF
 Nicotine Sublingual Tablets, NPF
 Nicotine Transdermal Patches, NPF
 Nystatin Oral Suspension, BP
 Olive Oil Ear Drops, BP
 Paracetamol Oral Suspension, BP (includes 120 mg/5 mL and 250 mg/5 mL strengths—both of which are available as sugar-free formulations)
¹Paracetamol Tablets, BP
¹Paracetamol Tablets, Soluble, BP (includes 120-mg and 500-mg tablets)
 Permethrin Cream, NPF
 Phosphates Enema, BP
 Povidone–Iodine Solution, BP
 Senna Oral Solution, NPF
 Senna Tablets, BP
 Senna and Ispaghula Granules, NPF
 Sodium Chloride Solution, Sterile, BP
 Sodium Citrate Compound Enema, NPF
 Sodium Picosulfate Capsules, NPF
 Sodium Picosulfate Elixir, NPF
 Spermicidal contraceptives as listed below:
 Gygel[®] Contraceptive Jelly
 Sterculia Granules, NPF
 Sterculia and Frangula Granules, NPF
 Titanium Ointment, BP
 Water for Injections, BP
 Zinc and Castor Oil Ointment, BP
 Zinc Oxide and Dimeticone Spray, NPF
 Zinc Oxide Impregnated Medicated Bandage, NPF
 Zinc Oxide Impregnated Medicated Stocking, NPF
 Zinc Paste Bandage, BP 1993
 Zinc Paste and Ichthammol Bandage, BP 1993

Appliances and Reagents (including Wound Management Products)

Community Practitioner Nurse Prescribers in England, Wales and Northern Ireland can prescribe any appliance or reagent in the relevant Drug Tariff. In the Scottish Drug Tariff, Appliances and Reagents which may **not** be prescribed by Nurses are annotated **Nx**.

Appliances (including Contraceptive Devices²) as listed in Part IXA of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 3 (Appliances) and Part 2 (Dressings) of the Scottish Drug Tariff)

Incontinence Appliances as listed in Part IXC of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 5 of the Scottish Drug Tariff)

Stoma Appliances and Associated Products as listed in Part IXC of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 6 of the Scottish Drug Tariff)

Chemical Reagents as listed in Part IXR of the Drug Tariff (Part II of the Northern Ireland Drug Tariff, Part 9 of the Scottish Drug Tariff)

The Drug Tariffs can be accessed online at:
 National Health Service Drug Tariff for England and Wales:
www.ppa.org.uk/ppa/edt_intro.htm
 Health and Personal Social Services for Northern Ireland Drug Tariff:
www.dhsspsni.gov.uk/pas-tariff
 Scottish Drug Tariff: www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

1. Max. 96 tablets; max. pack size 32 tablets

2. Nurse Prescribers in Family Planning Clinics—where it is not appropriate for nurse prescribers in family planning clinics to prescribe contraceptive devices using form FP10(P) (forms FP10(CN) and FP10(PN), or when available WP10CN and WP10PN, in Wales), they may prescribe using the same system as doctors in the clinic

Non-medical prescribing

A range of non-medical healthcare professionals can prescribe medicines for patients as either Independent or Supplementary Prescribers.

Independent prescribers are practitioners responsible and accountable for the assessment of patients with previously undiagnosed or diagnosed conditions and for decisions about the clinical management required, including prescribing. They are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved non-proprietary name.

Supplementary prescribing is a partnership between an independent prescriber (a doctor or a dentist) and a supplementary prescriber to implement an agreed Clinical Management Plan for an individual patient with that patient's agreement.

Independent and Supplementary Prescribers are identified by an annotation next to their name in the relevant professional register.

Information and guidance on non-medical prescribing is available on the Department of Health website at www.gov.uk/government/news/nurse-and-pharmacist-independent-prescribing-changes-announced.

For information on the mixing of medicines by Independent and Supplementary Prescribers, see *Mixing of medicines prior to administration in clinical practice—responding to legislative changes*, National Prescribing Centre, May 2010 (available at www.npc.nhs.uk/improving_safety/mixing_meds/resources/mixing_of_medicines.pdf).

For information on the supply and administration of medicines to groups of patients using Patient Group Directions, see p. 3.

Nurses

Nurse Independent Prescribers (formerly known as Extended Formulary Nurse Prescribers) are able to prescribe any medicine for any medical condition.

Nurse Independent Prescribers are able to prescribe, administer, and give directions for the administration of Schedule 2, 3, 4, and 5 Controlled Drugs. This extends to diamorphine, dipipanone, or cocaine for treating organic disease or injury, but not for treating addiction.

Nurse Independent Prescribers must work within their own level of professional competence and expertise.

For information on prescribing from the Nurse Prescribers' Formulary for Community Practitioners, see Nurse Prescribers' Formulary for Community Practitioners p. 828.

Pharmacists

Pharmacist Independent Prescribers can prescribe any medicine for any medical condition.

They are also able to prescribe, administer, and give directions for the administration of Schedule 2, 3, 4, and 5 Controlled Drugs. This extends to diamorphine, dipipanone, or cocaine for treating organic disease or injury, but not for treating addiction.

Pharmacist Independent Prescribers must work within their own level of professional competence and expertise.

Optometrists

Optometrist Independent Prescribers can prescribe any licensed medicine for ocular conditions affecting the eye and the tissues surrounding the eye, except Controlled Drugs or medicines for parenteral administration. Optometrist Independent Prescribers must work within their own level of professional competence and expertise.

Index of manufacturers

The following is an alphabetical list of manufacturers and other companies referenced in the BNF, with their medicines information or general contact details. For information on 'special-order' manufacturers and specialist importing companies see p. 840.

3M

3M Health Care Ltd
Tel: (01509) 611 611

A&H

Allen & Hanburys Ltd
See GSK

A1 Pharmaceuticals

A1 Pharmaceuticals Plc
Tel: (01708) 528 900
Email: sales@a1plc.co.uk

Abbott

See AbbVie

Abbott Healthcare

Abbott Healthcare Products Ltd
Tel: (023) 8046 7000
Email: medinfo.shl@abbott.com

AbbVie

AbbVie Ltd
Tel: (01628) 561 090
Email: ukmedinfo@abbvie.com

Abraxis

Abraxis BioScience Ltd
Tel: (020) 7081 0850
Email: abraxismedical@idispharma.com

Acorus

Acorus Therapeutics Ltd
Tel: (01244) 625 152

Actavis

Actavis UK Ltd
Tel: (01271) 311 257
Email: medinfo@actavis.co.uk

Actelion

Actelion Pharmaceuticals UK Ltd
Tel: (020) 8987 3333
Email: medinfo_uk@actelion.com

Activa

Activa Healthcare
Tel: 0845 060 6707
Email: advice@activahealthcare.co.uk

Adienne

Adienne Pharma and Biotech
Tel: 0039 (0) 335 873 8731

ADI Medical

ADI Medical UK
Tel: (01628) 485159
Email: info@adimedical.co.uk

Advanced Medical Solutions

Advanced Medical Solutions Group Plc
Tel: (01606) 863 500

Advancis

Advancis Medical Ltd
Tel: (01623) 751 500
Email: info@advancis.co.uk

Advantech Surgical

Advantech Surgical Ltd
Tel: 0845 130 5866
Email: customerservice@newgel.co.uk

Aegerion

Aegerion Pharmaceuticals Ltd
Tel: 00800 2343 7466
Email: medinfo.emea@aegerion.com

AgaMatrix

AgaMatrix Europe Ltd
Tel: (01235) 838 639
Email: info@wavesense.co.uk

Agepha

Agepha GmbH
Tel: (020) 3239 6241
Email: uk@agepha.com

Aguetant

Aguetant Ltd
Tel: (01934) 835 694
Email: info@aguettant.co.uk

Air Products

Air Products plc
Tel: 0800 373 580

Alan Pharmaceuticals

Alan Pharmaceuticals
Tel: (020) 7284 2887

Alcon

Alcon Laboratories (UK) Ltd
Tel: (01276) 673 311
Email: gbmedicaldepartment@alcon.com

Alexion

Alexion Pharma UK Ltd
Tel: (01932) 359 220
Email: alexion.uk@alxn.com

Alimera

Alimera Sciences Limited
Tel: 0800 019 1253
Email: medicalinformation@alimerasciences.com

Alissa

Alissa Healthcare
Tel: (01489) 780 759
Email: enquiries@alissahealthcare.com

ALK-Abelló

ALK-Abelló (UK) Ltd
Tel: (0118) 903 7940
Email: info@uk.alk-abello.com

Alkopharma

Alkopharma Srl
Tel: (0041) 277 206 969
Email: regulatory@alkopharma.com

Allergan

Allergan Ltd
Tel: (01628) 494 026

Allergy

Allergy Therapeutics Ltd
Tel: (01903) 844 702

Alliance

Alliance Pharmaceuticals Ltd
Tel: (01249) 466 966
Email: info@alliancepharma.co.uk

Almirall

Almirall Ltd
Tel: 0800 008 7399
Email: medinfouk@almirall.com

Altacor

Altacor Ltd
Tel: (01223) 421 411
Email: info@altacor-pharma.com

AMCo

Amdipharm Mercury Company Ltd
Tel: 08700 70 30 33
Email: medicalinformation@amcolim-lited.com

Amgen

Amgen Ltd
Tel: (01223) 420 305
Email: gbinfo@amgen.com

AMO

Abbot Medical Optics
Tel: 0800 376 7950

Amred

Amred Healthcare Ltd
Tel: (0330) 333 0079
Email: info@amredhealthcare.com

Apollo Medical

Apollo Medical Technologies Ltd
Tel: (01636) 831 201
Email: supercheck2@btinternet.com

Archimed

Archimed
Tel: 0800 756 9951
Email: enquiries@archimed.co.uk

Archimedes

Archimedes Pharma UK Ltd
Tel: (0118) 931 5094
Email: medicalinformationuk@archimedespharma.com

Arctic Medical

Arctic Medical Ltd
Tel: (01303) 277 751
Email: sales@arcticmedical.co.uk

Ardana

Ardana Bioscience Ltd
Tel: (0131) 226 8550

ARIAD

ARIAD Pharma UK Ltd
Tel: 0800 0002 7423
Email: eumedinfo@ariad.com

Ark Therapeutics

Ark Therapeutics Group Plc
Tel: (020) 7388 7722
Email: info@arktherapeutics.com

Aspen

Aspen
Tel: 0800 008 7392
Email: aspenglobal@professionalinformation.co.uk

Aspen Medical

Aspen Medical Europe Ltd
Tel: (01527) 587 728
Email: customers@aspenmedicaleurope.com

AS Pharma

AS Pharma Ltd
Tel: 0870 066 4117
Email: info@aspharma.co.uk

Aspire

Aspire Pharma Ltd
Tel: (01730) 231 148
Email: info@aspirepharma.co.uk

Astellas

Astellas Pharma Ltd
Tel: (020) 3379 8000
Email: medinfo.gb@astellas.com

AstraZeneca

AstraZeneca UK Ltd
Tel: 0800 783 0033
Email: medical.informationuk@astrazeneca.com

Auden Mckenzie

Auden Mckenzie (Pharma Division) Ltd
Tel: (01895) 627 420

Auxilium

Auxilium
Tel: 0845 017 2315
Email: auxilium@pilglobal.com

Axcan

Axcan Pharma SA
Tel: (0033) 130 461 900

AYMES

AYMES International Ltd
Tel: 0845 6805 496
Email: info@aymes.com

Ayrton Saunders

Ayrton Saunders Ltd
Tel: (0151) 709 2074
Email: info@ayrtons.com

BAP

BAP Medical UK Ltd
Tel: 0844 879 7689

Bard

Bard Ltd
Tel: (01293) 527 888

Basilea

Basilea Pharmaceuticals Ltd
Tel: (01483) 790 023
Email: ukmedinfo@basilea.com

Bausch & Lomb

Bausch & Lomb UK Ltd
Tel: (01748) 828 864
Email: medicalinformationuk@bausch.com

Baxter

Baxter Healthcare Ltd
Tel: (01635) 206 345
Email: surecall@baxter.com

Bayer

Bayer Healthcare Pharmaceuticals
Tel: (01635) 563 000
Email: medical.information@bayer.co.uk

Bayer Consumer Care

See Bayer

Bayer Diabetes Care

See Bayer

Bayer Diagnostics

See Bayer

BBi Healthcare

BBi Healthcare
Tel: (01792) 229 333
Email: info@bbihealthcare.com

B. Braun

B. Braun Medical Ltd
Tel: (0114) 225 9000
Email: info.bbmu@bbraun.com

Beacon

Beacon Pharmaceuticals Ltd
Tel: (01892) 600 930
Email: info@beaconpharma.co.uk

Beiersdorf

Beiersdorf UK Ltd
Tel: (0121) 329 8800

Besins

Besins Healthcare (UK) Ltd
Tel: (01748) 828 789
Email: information@besins-healthcare.com

BHR

BHR Pharmaceuticals Ltd
Tel: (024) 7637 7210
Email: info@bhr.co.uk

Biogen

Biogen Idec Ltd
Tel: 0800 008 7401

Biolitec

Biolitec Pharma Ltd
Tel: (00353) 1463 7415

BioMarin

BioMarin Europe Ltd
Tel: (020) 7420 0800
Email: biomarin-europe@bmrn.com

BioMondé

BioMondé
Tel: 0845 230 1810
Email: info@biomonde.com

Biotest UK

Biotest (UK) Ltd
Tel: (0121) 733 3393
Email: medicinesinformation@biotes-tuk.com

Blackwell

Blackwell Supplies Ltd
Tel: (01634) 877 620

BOC

BOC Medical
Tel: 0800 111 333

Boehringer Ingelheim

Boehringer Ingelheim Ltd
Tel: (01344) 424 600
Email: medinfo@bra.boehringer-ingel-heim.com

Boots

The Boots Company PLC
Tel: (0115) 959 5165

BPC 100

BPC 100 Ltd
Tel: 01942 852085

BPL

Bio Products Laboratory Ltd
Tel: (020) 8957 2255
Email: medinfo@bpl.co.uk

Bray

Bray Healthcare
Tel: (01367) 240 736
Email: info@bray-healthcare.com

Bristol-Myers Squibb

Bristol-Myers Squibb Pharmaceuticals Ltd
Tel: (01895) 523 000
Email: medical.information@bms.com

Britannia

Britannia Pharmaceuticals
Tel: 0870 851 0207
Email: enquiries@medinformation.co.uk

BSN Medical

BSN Medical Ltd
Tel: 0845 122 3600

BTG

BTG International Ltd
Tel: (0207) 575 0000
Email: medical.services@btgplc.com

Bullen

Bullen Healthcare
Tel: 0800 269 327

Cambridge Medical Aesthetics

Cambridge Medical Aesthetics Ltd
Tel: (01733) 396171
Email: info@cambridgemedicalaes-thetics.com

Cambridge Sensors

Cambridge Sensors Ltd
Tel: (01480) 482 920
Email: sales-orders@cs-limited.co.uk

CareFusion

CareFusion UK 244 Ltd
Tel: 0800 043 7546
Email: enquiries@chloraprep.co.uk

Casen-Fleet

Casen-Fleet
Tel: (0034) 913 518 800

C D Medical

C D Medical Ltd
Tel: (01942) 816 184

Celgene

Celgene Ltd
Tel: 0844 801 0045
Email: medinfo.uk.ire@celgene.com

Cephalon

Cephalon Ltd
Tel: 0800 783 4869
Email: ukmedinfo@cephalon.com

Chanelle Medical

Chanelle Medical UK Ltd
Tel: (01233) 822 297

Chattam UK

Chattam UK Ltd
Tel: (01256) 844 144

Chefaro UK

Chefaro UK Ltd
Tel: (01748) 828 860
Email: info@omegapharma.co.uk

Chemidex

Chemidex Pharma Ltd
Tel: (01784) 477 167
Email: info@chemidex.co.uk

Chiesi

Chiesi Ltd
Tel: (0161) 488 5555
Email: medinfo@chiesi.uk.com

CHS

Cambridge Healthcare Supplies Ltd
Tel: (01953) 607 856
Email: customerservices@cambridge-healthcare.co.uk

Chugai

Chugai Pharma UK Ltd
Tel: (020) 8987 5680

Clement Clarke

Clement Clarke International Ltd
Tel: (01279) 414 969
Email: resp@clement-clarke.com

Clinigen

Clinigen Group Plc
Tel: (01748) 828 375
Email: clinigen@professionalinformation.co.uk

CliniMed

CliniMed Ltd
Tel: (01628) 535 250

Clinisupplies

Clinisupplies Ltd
Tel: (020) 8863 4168
Email: info@clinisupplies.co.uk

Colgate-Palmolive

Colgate-Palmolive Ltd
Tel: (01483) 302 222

Coloplast

Coloplast Ltd
Tel: (01733) 392 000

Community

Community Foods Ltd
Tel: (020) 8450 9411
Email: email@communityfoods.co.uk

Complan Foods

Complan Foods Ltd
Tel: (020) 7395 7565

Consilient

Consilient Health UK Ltd
Tel: (020) 8956 2310
Email: drugsafety@consilienthealth.com

ConvaTec

ConvaTec Ltd
Tel: (01895) 628 400

Co-Pharma

Co-Pharma Ltd
Tel: 0870 851 0207

Correvio

Correvio GmbH
Tel: (020) 3002 8114
Email: info@correvio.com

Covidien

Covidien UK Commercial Ltd
Tel: (01329) 224 226

Cow & Gate

Cow & Gate
Tel: 0845 762 3624

Cranage

Cranage Healthcare Ltd
Tel: (01477) 549 392
Email: db@cranagehealth.com

Crawford

Crawford Healthcare Ltd
Tel: (01565) 654 920

Crescent

Crescent Pharma
Tel: (01256) 772 730
Email: info@crescentpharma.com

Crucell

Crucell (UK) Ltd
Tel: 0844 800 3907
Email: info@crucell.co.uk

CSL Behring

CSL Behring UK Ltd
Tel: (01444) 447 400
Email: medinfo@cslbehrling.com

CTI

CTI Life Sciences Ltd
Tel: (01628) 643 974

Daiichi Sankyo

Daiichi Sankyo UK Ltd
Tel: (01753) 482 771
Email: medinfo@daiichi-sankyo.co.uk

Danetre

Danetre Health Products Ltd
Tel: (01327) 310 909
Email: enquiries@danetrehealthproducts.com

DDD

DDD Ltd
Tel: (01923) 229 251

Dee

Dee Pharmaceuticals Ltd
Tel: (01978) 661993
Email: enquiries@deepharmaceuti-calsltd.co.uk

Dental Health

Dental Health Products Ltd
Tel: (01622) 749 222

Dentsply

Dentsply Ltd
Tel: (01932) 837 279

Dermal

Dermal Laboratories Ltd
Tel: (01462) 458 866

Dermato Logical

Dermato Logical Ltd
Tel: (0208) 449 2931
Email: enquiries@aqua-max.co.uk

Dermatronics

Dermatronics Ltd
Tel: (01480) 462 910
Email: sales@dermatronics.co.uk

Derma Sciences Europe

Derma Sciences Europe Ltd
Tel: (01628) 625 916
Email: cs@dermasciences.com

Derma UK

Derma UK Ltd
Tel: (01462) 733 500
Email: info@dermauk.co.uk

Desitin

Desitin Pharma Ltd
Tel: (01483) 688 240
Email: medinfo@desitin.co.uk

DeVilbiss

DeVilbiss Healthcare UK Ltd
Tel: (01384) 446 688

Dexcel

Dexcel-Pharma Ltd
Tel: (01327) 312 266
Email: office@dexcelpharma.co.uk

DHP Healthcare

DHP Healthcare Ltd
Tel: (01622) 749 222
Email: sales@dhphealthcare.co.uk

DIME

DIME
Tel: (01483) 715 008
Email: info@dime-med.com

Dreamskin

Dreamskin Health Ltd
Tel: (01707) 228 688

Dr Falk

Dr Falk Pharma UK Ltd
Tel: (01628) 536 600

Drossa

Drossa Ltd
Tel: (020) 3393 0859
Email: info@drossa.co.uk

Durbin

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Special-order Manufacturers

Unlicensed medicines are available from 'special-order' manufacturers and specialist-importing companies; the MHRA maintains a register of these companies at <http://tinyurl.com/cdskle>

Licensed **hospital manufacturing units** also manufacture 'special-order' products as unlicensed medicines, the principal NHS units are listed below. A database (*Pro-File*; www.pro-file.nhs.uk) provides information on medicines manufactured in the NHS; access is restricted to NHS pharmacy staff.

The Association of Pharmaceutical Specials Manufacturers may also be able to provide further information about commercial companies (www.apsm-uk.com).

The MHRA recommends that an unlicensed medicine should only be used when a patient has special requirements that cannot be met by use of a licensed medicine

As well as being available direct from the hospital manufacturer(s) concerned, many NHS-manufactured Specials may be bought from the Oxford Pharmacy Store, owned and operated by Oxford Health NHS Foundation Trust.

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Index

Principal page references are printed in **bold** type. Proprietary (trade) names and names of organisms are printed in *italic* type; where the BNF does not include a full entry for a branded product, the non-proprietary name is shown in brackets

A

- A2A Spacer*, 143
Abacavir, 314, **315**, 316
 lamivudine and zidovudine with, 316
 lamivudine with, 315
Abatacept, 514, **515**
 Abbreviations
 latin, *inside back cover*
 symbols and, *inside back cover*
 units, 4
 Abdominal surgery, antibacterial prophylaxis, 259
Abelcet, 310
 Abetalipoproteinaemia, 490
Abidec, 492
Abilify, 178
Able Spacer, 143
 Abscess, dental, 255
 Absence seizures, 219
Acanthamoeba keratitis, 525
 contact lenses, 540
Acarbose, 366
 Acaricides, 597
 ACBS
 foods, 771
 toilet preparations, 818
Accolate, 151
Accrete D3, 489
Accu-Chek products, 370
Accuhaler
 Flixotide, 148
 Seretide, 149
 Serevent, 139
 Ventolin, 138
 ACE inhibitors, 98
 diuretics with, 99
 heart failure, 99
 renal function, 99
Acea, 593
 Acetaminophen *see* Paracetamol
 Acetazolamide
 diuretic, 81
 epilepsy, 236, **533**
 glaucoma, 531, **533**, 534
 intracranial pressure, raised, **533**
 Acetic acid, otitis externa, 542
 Acetylcholine, **539**
 Acetylcysteine
 cystic fibrosis, 164
 eye, 536
 meconium ileus, 164
 mucolytic, **164**
 paracetamol poisoning, 26, **27**
 Acetylsalicylic acid *see* Aspirin

- Aciclovir
 herpes simplex, **326**
 eye, 326, **527**
 genital, 400, 596
 labialis, 596
 skin, **597**
 herpes stomatitis, 551
 herpes zoster, **326**
 varicella-zoster, **326**
 Acid aspiration, prophylaxis, 635
Acidex, 37
 Acidosis
 lactic, 315
 metabolic, 466, 470
Acitretin, 574, **577**, 578
Acnamino MR, 279
 Acne, 580
 infantile, 580, 585
 systemic treatment, 584
 topical treatment, 581
Acnecide, 581
Acnecin (co-cyprindiol), 584
Acrivastine, **152**
 Acrodermatitis enteropathica, 483
 ACTH *see* Corticotropin, 387
Actidose-Aqua Advance, 25
Actilyse preparations, 120
 Actinic keratoses, 589
 Actinomycin D *see* Dactinomycin, **426**
Actiq, 207
 Activated charcoal, 24, **25**
Active, 370, 371
Actonel, 396
 Once a Week, 396
Actrapid, 359
Acular, 540
ACWY Vax, 621
 Acyclovir *see* Aciclovir
Adalat preparations, 106
 Adalimumab, 516
 Crohn's disease, 48, 54, **55**
 rheumatic diseases, 514, **515**
 Adapalene, 582, **583**
 benzoyl peroxide with, 583
Adcal, 478
Adcal-D3 preparations, 489
Adcortyl Intra-articular/Intradermal, 511
Add-Ins, 815
Addiphos, 474
 Addison's disease, 375
 Additives *see* Excipients
Additrac, 474
 Adefovir, 329
Adenocor, 83
Adenoscan, 83
 Adenosine, **82**, 83
 Adenovirus, 332
 ADH *see* Antidiuretic hormone, 390
 ADHD *see* Attention deficit hyperactivity disorder, 188
 Adhesive, tissue, 599
Adipine preparations, 106
Adoport, 441
 Adrenal function test, 387
 Adrenal insufficiency, 375
 Adrenal suppression
 metyrapone, 396
 surgery, 377
 systemic corticosteroids, 377
 topical corticosteroids, 564
 Adrenaline
 anaphylaxis, 158, **159**, 160
 bradycardia, 81
 croup, 135
 hypotension, 112
 infusion table (neonatal), 824
 local anaesthesia, 654, 656
 palliative care, capillary bleeding, 17
 self administration, 159
 Adrenergic neurone blocking drugs, 97
 Adrenoceptor agonists, 135
 Adsorbents
 gastro-intestinal, 45
 poisoning, 24
Advagraf, 443
Advantage Plus, 370
Advate (factor VIII fraction), 123
 Adverse reactions
 prevention of, 12
 reporting, 11
 Advisory Committee on Borderline Substances *see* ACBS
 Advisory labels *see* Cautionary and advisory labels
AeroChamber Plus, 143
 Agalsidase
 alfa, **495**
 beta, **495**
 Agammaglobulinaemia, congenital, replacement therapy, 628
Agrippal, 617
 AIDS
 treatment, 313
 vaccines and, 605
Airomir preparations, 138
AirSalb (salbutamol), 138
AirZone, 142
Aizea (desogestrel), 408
Aknemin (minocycline), 279
Aknemycin Plus, 583
 Albendazole
 hookworms, 353
 hydatid disease, 353
 larva migrans, 354
 strongyloidiasis, 354
 Albumin solution, **471**
Albunorm preparations (albumin), 471
Albustix, 372
Albuterol *see* Salbutamol
 Alclometasone dipropionate, 567, 568
 Alcohol
 poisoning by, 25
 presence of, 3
 skin, 600
 Aldactone, 80
Aldara, 587
 Aldioxa, 602
 Aldosterone antagonists, 79, 80
Aldurazyme, 497

- Alemtuzumab, 444
 Alendronate sodium *see*
 Alendronic acid, **394**, 395
 Alendronic acid, **394**, 395
 Alfalcidol, **488**
 Alfentanil, 204, **645**, 646
 Alginate-containing antacids, 36
 Alglucosidase alfa, **497**, 498
Alicalm, 797
 Alimemazine
 allergic disorders, 152, **154**, 155
 premedication, 154, 642
 Alkalinisation of urine, 417
Alkeran, 425
 Alkylating drugs, 424
Alkyron, 186
 Allergy
 allergen immunotherapy, 156
 anaphylaxis, 158
 antiepileptic hypersensitivity syndrome, 217
 antihistamines, 151
 conjunctivitis, 528
 corticosteroids in, 377
 food, 56
 rhinitis, 152, 545
 Allopurinol, **422**
 Almond oil, ear, 544, 545
Alomide, 529
 Alpha tocopherol, **490**
 Alpha tocopheryl acetate, **490**
 Alpha₂-adrenoceptor stimulants
 cardiovascular, 96
 eye, 533, 539
 Alpha-adrenoceptor blocking drugs, 97
 urinary tract, 415
 Alpha-blockers *see* Alpha-adrenoceptor blocking drugs
Alphaderm, 567
Alphanate (factor VIII fraction), 122
AlphaNine (factor IX fraction), 123
Alphosyl 2 in 1, 590
Alprostadil, **130**
 infusion table (neonatal), 824
Altacite Plus, 36
Altargo, 592
Alteplase, **120**
 Alternative medicine, 2
Althéra, 792
Alu-Cap, 481
 Aluminium acetate, ear, 541, **542**
 Aluminium chloride, **602**
 Aluminium hydroxide
 antacid, **35**, 36
 simeticone with, 36
 hyperphosphataemia, 481
Alverine, **39**
Alvesco, 148
Amantadine, 330
Ambirix, 613
Ambisome, 310
 leishmaniasis, 348
Amethocaine *see* Tetracaine
Ametop, 659
 Amfetamines
 abuse, 9
 poisoning by, 30
Amias, 102
 Amidotrizoates, 64, 65
 Amikacin, 280, **282**, 283
 tuberculosis, 296
Amikin, 283
Amilamont (amiloride), 79
 Amiloride, **79**
 furosemide with, 80
 hydrochlorothiazide with, 80
 Amino acids
 ACBS, 811, 812, 813, 814, 815, 817
 intravenous nutrition, 473
 Aminobenzoic acid, 485
 Aminoglycosides
 ear, 541, 544
 eye, 524
 systemic, 280
 Aminophylline, 75, 140, **141**, 142
 see also Theophylline
 Aminosalicylates, 47, 49
 Amiodarone, 81, 82, **83**, 84
 Amisulpride, 171, **177**
 Amitriptyline
 depression, **185**
 neuropathic pain, **185**, 213
 palliative care, 16
 nocturnal enuresis, **185**
Amix (amoxicillin), 265
 Amlodipine, **104**, 105
 see also Calcium-channel blockers
Amlostin (amlodipine), 104
Ammonaps, 500
 Ammonia, poisoning by, 32
 Amoebiasis, 347
 Amoebic
 abscess, 347
 dysentery, 347
 Amoebicides, 347
Amoram (amoxicillin), 265
 Amorolfine, **594**
 Amoxicillin, **265**
 clavulanic acid with, 266
 Helicobacter pylori eradication, 41
 pneumococcal infection prophylaxis, 259
Amoxident (amoxicillin), 265
Amoxil preparations, 265
 Amoxycillin *see* Amoxicillin
 Amphetamines *see* Amfetamines
 Amphotericin
 eye, 536
 infusion
 lipid formulation, 309, 310
 liposomal, 310
 leishmaniasis, 348
 systemic, 304, 305, **309**
 Ampicillin, 264, **265**, 266
 flucloxacillin with [co-fluampicil], 264
Amsacrine—*discontinued*
Amsidine—*discontinued*
Anabact, 593
 Anabolic steroids, 387
 anaemias, 454
 Anaemias, 448
 aplastic, 454
 chronic renal failure, 454
 haemolytic, 454, 459
 hypoplastic, 454
 iron-deficiency, 448
 megaloblastic, 452
 sideroblastic, 454
 Anaesthesia
 analgesics, 645
 anticholinesterases, 651
 anticoagulants, oral and, 635
 antidepressants and, 635
 antimuscarinics, 640
 antiviral drugs and, 635
 corticosteroids, 377, 634
 dental practice, 635
 diuretics, 635
 general, 634
 inhalational, 638
 intravenous, 635
 local, 654
 adrenaline with, 654
 dental, 655
 eye, 535
 mouth, 549
 neuropathic pain, 213
 rectal, 65
 vasoconstrictors with, 654
 local toxicity, 655
 muscle relaxants, 647
Anagrelide, **460**
 Anal fissure, 67
 Analeptics, 161
 Analgesics
 compound, 200
 non-opioid, 199
 postoperative, 645
 NSAIDs, 199, 504
 anaesthesia, 645
 palliative care, 16
 poisoning by, 25
 rheumatic diseases, 504
 opioid, 203
 anaesthesia, 645
 cough suppressants, 166
 dependence on, 9
 equivalent doses, 17
 neuropathic pain, 213
 obstetric pain, 204
 palliative care, 16
 poisoning by, 27
Anapen preparations—*discontinued*
 Anaphylactic shock, 158
 Anaphylaxis, 158
Ancora 375 devices, 412
Ancotil, 312
 Ancylostomiasis, 353
Androcur, 386
 Androgens, 384
Anectine, 651
Anexate—*discontinued*
Angilol (propranolol), 88
 Angioedema, 160
 Angiotensin-converting enzyme inhibitors *see* ACE inhibitors

- Angiotensin-II receptor antagonists, 101
- Angular cheilitis, 552, 565
- Anhydrol Forte*, 602
- Anogenital warts, 587
- Anorectics, 191
- Anorexia, palliative care, 17
- Antacids, 35
- palliative care, 18
 - sodium content, 35
 - surgery, 635
- Antazoline, **528**, 529
- Antepsin*, 43
- Anterior uveitis, 530
- Anthelios*, 588
- Anthelmintics, 352
- Anthracycines, 426
- Anthralin *see* Dithranol
- Anthraquinones, 58
- Anthrax, 301
- vaccine, 608
- Anti-androgens, 385
- Anti-arrhythmic drugs, 81
- Antibacterials
- acne, 582, 584
 - diarrhoea, 45
 - infections
 - ear, 541
 - eye, 524
 - oral, 247
 - skin, 591
 - vaginal, 398 - policies, 247
 - principles for selecting, **247**
 - prophylaxis, surgery, 260
 - prophylaxis (table), 258
 - therapy, initial (table), 248
- Antibiotic-associated colitis *see* *Clostridium difficile*
- Antibiotics *see* Antibacterials
- Anticholinergic drugs *see* Antimuscarinics
- Anticholinergic syndrome, 640
- Anticholinesterases, 518
- anaesthesia, 651
- Anticoagulant treatment booklets, 117
- Anticoagulants
- oral, 116
 - anaesthesia, 635
 - reversal, 117
 - surgery, 635 - parenteral, 113
- Anticonvulsants *see* Antiepileptics
- Antidepressants
- anaesthesia, 635
 - choice, 183
 - hyponatraemia and, 184
 - monoamine-oxidase inhibitors, 186
 - poisoning by, 28
 - serotonin re-uptake inhibitors, 183, 186
 - surgery, 635
 - tricyclic, 184
 - enuresis, 417
 - withdrawal, 184
- Antidiabetic drugs
- insulin, 356
 - oral, 364
- Antidiarrhoeal drugs *see* Diarrhoea
- Antidiuretic hormone, 390
- Antiemetics, 192
- cytotoxic therapy and, 420
 - migraine, 213, 215
 - palliative care, 18
- Antiepileptics, 216, 219
- breast-feeding and, 218
 - hypersensitivity syndrome, 217
 - pregnancy and, 218
 - surgery, 635
- Antifibrinolytic drugs, 121
- Antifungal drugs, 304
- anogenital, 398
 - oropharyngeal, 551
 - skin, 594
- Antigardial drugs, 348
- Antihepatitis B immunoglobulin, 630, 631
- Antihistamines, 151
- breast-feeding, 152
 - cough preparations, 166
 - eczema, 572
 - eye, 528
 - hypnotic, 169
 - insomnia, 152
 - migraine, 215
 - nasal allergy, 545
 - nausea and vertigo, 193
 - nausea and vomiting, 192, 193
 - pregnancy, 152
 - skilled tasks and, 152, 154
 - skin, 563
- Antihypertensives
- ACE inhibitors, 98
 - adrenergic neurone blockers, 97
 - alpha-blockers, 97
 - angiotensin-II receptor antagonists, 101
 - beta-blockers, 86
 - calcium-channel blockers, 104
 - centrally-acting, 96
 - vasodilator, 91
- Anti-inflammatory analgesics *see* Analgesics, NSAIDs
- Antilymphocyte immunoglobulin, 454
- Antimalarials, 334, 512
- Antimanic drugs, 181
- Antimetabolites, 428
- Antimigraine drugs, 213
- Antimotility drugs, 45
- Antimuscarinics
- antipsychotics and, 172
 - bronchodilator, 139
 - dystonias, 241
 - eye, 530
 - gastro-intestinal, 38
 - premedication, 640
 - quaternary ammonium, 38
 - urinary tract, 415
- Antineoplastic drugs, 419
- see also* Cytotoxic drugs
- Antiperspirants, 602
- Antiplatelet drugs, 118
- Antiprotozoal drugs, 334
- Antipsychotics, 171
- depot injections, 181
 - equivalent doses, oral, 174
 - extrapyramidal symptoms, 172, 173
 - first-generation, 171
 - high doses (caution), 170
 - mania, 181
 - second-generation, 171
 - poisoning by, 30
 - withdrawal, 172
- Antirabies immunoglobulin, 631
- Antiretrovirals, **313**, 314, 324
- non-nucleoside reverse transcriptase inhibitors, 322
 - nucleoside reverse transcriptase inhibitors, 315
 - protease inhibitors, 319
- Antiseptics
- ACBS, 819
 - lozenges, 552
 - mouthwashes, 553
 - skin, 599
 - sprays, oropharynx, 552
- Antiserum, 607, 627
- Antispasmodics, 37
- Antitetanus immunoglobulin, 631
- Antithymocyte immunoglobulin, **438**
- Antithyroid drugs, 373
- Antituberculous drugs, 294
- Antitussives, 166
- Antivaricella-zoster immunoglobulin, 631, 632
- Antivenoms, 33
- Antiviral drugs, 313
- anaesthesia, 635
 - eye, 527
 - mouth, 551
 - skin, 596
 - surgery, 635
- Anugesic-HC*, 65
- Anusol* preparations, 66
- Anxiety
- antipsychotics, 171
 - palliative care, 17
 - treatment, 170, 184
- Anxiolytics, 168, 170
- APD *see* Pamidronate disodium, **395**
- Aphthous ulcers, 549
- Apidra*, 360
- Aplastic anaemia, 454
- Apnoea neonatal
- caffeine citrate, 161
- Appetite suppressants, 191
- Applications, definition, 557
- Apraclonidine, 533, **539**
- Apresoline*, 92
- Aprinox* (bendroflumethiazide), 76
- Aptamil Pepti* preparations, 792
- Aptivus*, 322
- Aquadrate*, 559
- Aquamax* preparations, 558, 561
- Aquamol*, 558
- Aquasol-A*, 484
- Aqueous cream, 558, 560

- Aqueous iodine oral solution, 374
- Arachis oil
 enema, 60
 presence of, 3
- Aragam, 630
- Aranesp preparations, 455
- Arcoxia, 508
- Aredia Dry Powder, 395
- Arginine
 urea cycle disorders, **498**
- Argipressin (synthetic vasopressin), 393
- Aripiprazole, 171, **177**
- Arovit, 484
- Arpicolin, 241
- Arrhythmias, **81**
 anti-arrhythmics, 81
 poisoning and, 23
 supraventricular, 72, 81
 ventricular, 81
- Artelac preparations, 536, 537, 538
- Artemether
 lumefantrine with, **342**
- Artenimol, piperazine with, **344**
- Artesunate, 335
- Arthritis
 juvenile idiopathic, 512
 rheumatic, 504
 septic, 255
- Arthrofen (ibuprofen), 508
- Arthroxen (naproxen), 510
- Articaine, **655**, 656
- Artificial saliva, 554
 palliative care, 18
- Artificial tears, 536
- Arzip (mycophenolate mofetil), 437
- AS Saliva Orthana, 554
- 5-ASA, 49
- Asacol preparations, 49, 50
- Ascaricides, 353
- Ascaris, 353
- Ascites, 79
- Ascorbic acid, 486, **487**
 iron excretion, 457
- Asmabec preparations, 146
- Asmanex, 150
- Asmasal preparations, 138
- Asparaginase, 432
- Aspart, insulin *see* Insulin aspart
- Aspartame, 475
 presence of, 3
- Aspergillosis, 304
- Aspiration, acid, prophylaxis, 635
- Aspirin
 antiplatelet, **119**
 Kawasaki disease, 119
- Asplenia
 Haemophilus influenzae type b (Hib)
 prophylaxis, 259
 vaccine, 612
 influenza vaccine, 616
 malaria, 336
 meningococcal vaccine, 612
 pneumococcal
 infection, 259
- Asplenia
 pneumococcal (*continued*)—
 vaccine, 622
 vaccines and, 607
- Asthma, 131, 132
 acute (table), 134
 allergen immunotherapy, 156
 beta₂ agonists, 135
 breast-feeding, 131
 chronic (table), 133
 exercise-induced, 135
 pregnancy, 131
 prophylaxis, 144, 150
 sympathomimetics, 135
- Astringents
 ear, 541
 skin, 599
- Atarax, 155
- Atazanavir, 314, **319**, 320
- Atenolol, 86, **88**
 see also Beta-adrenoceptor blocking drugs
 supraventricular tachycardia, 81
 thyrotoxicosis, 374
- Athlete's foot, 594
- Atimos Modulite, 136
- Ativan (lorazepam), 643
- Atomoxetine, **188**, 189
- Atonic seizures, 219
- Atorvastatin, 124, **125**
- Atovaquone
 malaria, 345
 pneumocystis pneumonia, **350**, 351
 proguanil with, 346
- Atracurium, **648**, 649
 infusion table (neonatal), 824
- Atrial fibrillation, 72, 81, 116
- Atrial flutter, 81
- Atriance, 430
- Atripila, 318
- Atropine sulfate
 anaesthesia, 640, 641
 bradycardia, 640
 anticholinesterases and, 652
 beta-blocker poisoning, 29
 eye, **530**
 organophosphorus poisoning, 32
- Atrovent preparations, 140
- Attention deficit hyperactivity disorder, 188
- Atypical antipsychotics, 171
 poisoning by, 30
- Atypical haemolytic uraemic syndrome, 459
- Augmentin preparations, 267, 268
- Aureocort, 572
- Autopen, 363
- Avamys, 547
- Avaxim, 613
- Aveeno preparations, 558, 561
- Aviva, 370
- Avloclor, 343
- Avoca, 587
- Avomine, 195
- AYMES Shake, 784
- Azactam, 277
- Azamune (azathioprine), 437
- Azathioprine
 auto-immune conditions, 513
 Crohn's disease, **53**
 eczema, 578
 inflammatory bowel disease, 48
 rheumatic disease, 513
 systemic lupus erythematosus, 513
 transplant rejection, **436**, 437
 ulcerative colitis, **53**
 vasculitis, 513
- Azelacic acid, 581, **582**
- Azelastine
 eye, 528, **529**
 nose, **545**
 fluticasone propionate with, 547
- Azidothymidine *see* Zidovudine
- Azithromycin, **284**, 285
 eye, 524, **525**
- Azopt, 534
- AZT *see* Zidovudine
- Aztreonam, **277**
- Azyter, 525

B

- Babyhaler, 143
- Bacillus Calmette-Guérin
 vaccines, **608**
- Bacitracin, polymyxin with, 592
- Baclofen
 chronic spasticity, **520**
 palliative care, 18
- Bacteroides fragilis infections
 antipseudomonal penicillins in, 268
 clindamycin in, 287
 metronidazole in, 299
- Bactroban, 592
 Nasal, 549
- Balance Activ Rx, 400
- Balanced Salt Solution, 538, 539
- Balneum preparations, 560, 561
- Balsalazide, 47, **49**
- Bandages
 medicated, 573
 tubular, 572
- Barbiturates, anaesthesia, 636
- Barkat products, 808, 809, 810
- Barrier preparations, 563
- Bartter's syndrome, 79
- Basiliximab, **438**, 439
- Bath additives
 antimicrobial with, 562
 coal tar, 576
 emollient, 561, 562
- Bazetham MR (tamsulosin), 415
- BCG vaccines, **608**
- Beclomethasone dipropionate
 asthma, 144, **146**
 chronic, 133
 mouth ulceration, 550
 nasal allergy, **546**
 skin, **568**
- Beclomethasone dipropionate *see* Beclomethasone dipropionate

*Becodisks—discontinued**Beconase* preparations, 546*Bedranol SR* (propranolol), 88

Bee sting allergy preparations, 156

Benadryl Allergy Relief, 152Bendroflumethiazide *see*Bendroflumethiazide, **76**Bendroflumethiazide, **76***BeneFIX* (factor IX fraction), 123*Benerva*, 486Benoxinate *see* Oxybuprocaine, **535**

Benzalkonium, 590

cetrimide with, 563

chlorhexidine with, 560

dimeticone with, 563

Benzathine benzylpenicillin, 253, 261

Benzhexol *see* Trihexyphenidyl, **241**

Benzodiazepines

antagonist, 653

anxiolytics, 168

clinical procedures, 642

epilepsy, 234

mania, 181

muscle spasm, 520

palliative care

anxiety, 17

insomnia, 18

poisoning by, 29

premedication, 642

Benzoic acid ointment,

compound, 594, 595

Benzoin tincture, compound, 166

Benzoyl peroxide

acne, 581

clindamycin with, 581

hydroxyquinoline with,

581

adapalene with, 583

Benzydamine, **550**

Benzyl alcohol, presence of, 3

Benzyl benzoate, 597

Benzylpenicillin sodium, 261, **262**Beractant, **162***Beriner*, 161*Beriplex P/N* (dried prothrombin complex), 122*Beta Prograne* (propranolol), 88Beta₂ agonists, 135

asthma, acute, 132

palliative care, 18

Beta-adrenoceptor blocking drugs

arrhythmias, 81, 82, 86

atrial fibrillation, 81

diuretics with, 86

eye, 531

heart failure, 86

hypertension, 86

poisoning by, 29

thyrotoxicosis, 87, 374

verapamil and, 107

Beta-adrenoceptor stimulants, asthma, 135

Beta-blockers *see* Beta-adrenoceptor blocking drugs*Betacap*, 568*Beta-Cardone*, 90

Betacarotene, 589

Betadine, 601*Betagan*, 532Betaine, **500**

Beta-lactamases, 261

Betamethasone

mouth, 550

skin, 568

systemic, 376, **380**

Betamethasone dipropionate

skin, 568

calcipotriol with, 575

clotrimazole with, 569

salicylic acid with, 568

Betamethasone sodium phosphate

ear, 542

eye, 528

inflammatory and allergic

disorders, 380

mouth, 550

nose, **546**, 549

neomycin with, 549

oral ulceration, 550

Betamethasone valerate

skin, 568

clioquinol with, 569

fusidic acid with, 569

neomycin with, 569

Betaxolol, **531**, 532*Betnesol*

ear, 542

eye, 528

inflammatory and allergic

disorders, 380

nose, 546

Betnesol-N

ear, 542

eye, 528

nose, 549

Betnovate preparations, 568*Betoptic*, 532*Bettamousse*, 568*Bexsero*, 621Bezafibrate, **128***Bezalip*, 128*BGStar* products, 370, 371*BiAlimenta* products, 809

Bicarbonate

intravenous, 470

oral, 466

see also Sodium bicarbonate

Biguanides, 366

Bilastine, **152**

Bile acid sequestrants, 69, 127

Bilharziasis, 353

Bimatoprost, 532

Bincrit, 455*BiNovum*, 407

Biosimilar medicines, 2

Biotène Oralbalance, 554Biotin, 485, **500**, 501*BioXtra*, 554Biphosphonates *see*

Biphosphonates

Bipolar disorder, 181

Birthmarks, ACBS, 819

Bisacodyl, 58

Bismuth subgallate, 65

Bisphosphonates

hypercalcaemia, 479

osteoporosis, 394

Bites

animal

prophylaxis of infection,

259

treatment of infection, 257

human

prophylaxis of infection,

259

treatment of infection, 257

snake, 33

Black triangle symbol, 12

Bladder

blood clot dissolution, 417

instillations

sodium chloride, 418

irrigations, 417

sodium chloride, 417

sodium citrate, 417

Bleeding

mucosal, palliative care, 18

variceal, 391

Bleo-Kyowa (bleomycin), 426Bleomycin, **426**

Blepharitis, 524

Blink Intensive Tears, 538

Blood products, 122, 123

Body surface area charts, *inside back cover*

Bone metabolism, drugs affecting, 393

Bone tumours, analgesia, 200

Bonefos, 396

Bone-marrow suppression,

cytotoxic drugs, 421

Bonjela (choline salicylate), 551Borderline substances *see* ACBSBosentan, **94***Botox*, 242

Botulinum antitoxin, 609

Botulinum toxin type A, **242**

hyperhidrosis, 602

Botulism antitoxin, 609

Bowel

cleansing preparations, 63

irrigation, 25

sterilisation, 280

Bradycardia, 81

anaesthesia, 640

Bramitob, 283

Breast-feeding

corticosteroids and, 379

epilepsy and, 218

prescribing in, 15

Breeze products, 370*Brevibloc*, 89*Brevinor*, 406*Brevoxyl*, 581*Brexidol*, 510*Bricanyl* preparations, 139*Bridion*, 652

Brimonidine, 533

Brimonidine, 533, **534***Broflex—discontinued**Brolene* preparations, 526

Bromocriptine, neuroleptic

malignant syndrome, 173

- Bronchodilators
 adrenoceptor agonist, 135
 antimuscarinic, 139
 compound, 142
 sympathomimetic, 135
 theophylline, 140
- Bronchopulmonary dysplasia, 75, 77
- Bronchospasm, 135
- Brucellosis, 277, 298
- Brufen* preparations, 508, 509
- Brugia malayi*, 354
- Buccastem*, 196
- Buccolam*, 238
- Bucizine, codeine and paracetamol with, 203
- Budelin Novolizer*, 147
- Budenofalk*, 52
- Budesonide
 asthma, 144, **147**
 chronic, 133
 formoterol with, 147
 bronchopulmonary dysplasia, 147
 croup, 135, 147
 inflammatory bowel disease, 47
 Crohn's disease, 52
 ulcerative colitis, 52
 nasal
 allergy, **546**
 polyps, **546**
- Bumetanide, **77**, 78
- Bupivacaine, **656**
 adrenaline with, 656
- Buprenorphine
 pain, 204, **205**
 palliative care, 16
 morphine equivalence, 17
 transdermal route, 17
- Buscopan*, 39
- Busilvex*, 424
- Buspirone, 170
- Busulfan, **424**
- Busulphan *see* Busulfan, **424**
- Butylcyanoacrylate, 599
- Butyrophenones, 171
- C**
- C1-esterase inhibitor, 160, **161**
- Cacit*, 478
- Cacit D3*, 489
- Caffeine citrate, **161**
- Calamine, 563, 564
- Calceos*, 489
- Calchan MR* (nifedipine), 106
- Calcichew*, 478
- Calcichew D3 preparations*, 489
- Calciferol, 487
- Calciferol *see* Ergocalciferol, 487, **488**
- Calcipotriol, 573, **574**
 betamethasone dipropionate with, 575
- Calcitonin, 393, **394**, 479
- Calcitriol
 psoriasis, 573, 574, **575**
 vitamin D deficiency, 487, **489**
- Calcium
 colecalciferol with, 489, 490
 ergocalciferol with, 487, 488
 supplements, 477, 478
- Calcium acetate, 482
- Calcium and vitamin D tablets, 488
- Calcium balance, maintenance, 393
- Calcium carbonate
 colecalciferol with, 489, 490
 hyperphosphataemia, **481**
- Calcium channel blockers *see* Calcium-channel blockers
- Calcium chloride, 479
- Calcium folinate, 422, 423, 452
- Calcium gluconate, 477, 478
- Calcium lactate, 478
- Calcium leucovorin *see* Calcium folinate, 422, 423, 452
- Calcium levofolinate, 422, 423
- Calcium levoleucovorin *see* Calcium levofolinate, 422, 423
- Calcium phosphate, 490
- Calcium polystyrene sulfonate, 465
- Calcium Resonium*, 465
- Calcium-500*, 478
- Calcium-channel blockers, 104
 dihydropyridines, 104
 poisoning by, 29
 pulmonary hypertension, 93
- Calcium-Sandoz*, 478
- Calcort*, 380
- Calfovit D3*, 490
- Calluses, 586
- Calmurid*, 560
- Calmurid HC*, 567
- Calogen preparations, 802, 804
- Caloreen*, 801
- Calprofen* (ibuprofen), 508
- Calshake*, 804
- Camcolit*, 183
- Camouflaging preparations, 589
- Campylobacter* enteritis, 248
- Canakinumab, **446**
 rheumatic diseases, 514, **516**
- Cancidas*, 311
- Candesartan, 101, **102**
- Candidiasis
 oropharyngeal, 304, 551
 perianal, 65
 skin, 594
 systemic, 304
 vaginal, **399**
 vulval, 398
 vulvovaginal, recurrent, 398
- Candidosis *see* Candidiasis
- Canesten*
 anogenital, 399
 ear, 543
 skin, 595
 HC, 567
- Cannabinoid, 198
- Cannabis, regulations, 9
- Capasal*, 590
- Capexion*, 441
- Capillary bleeding, palliative care, 17
- Capimune*, 439
- Caplenal* (allopurinol), 422
- Capoten*, 100
- Capreomycin, 296
- Caprilon*, 795
- Caprin* (aspirin), 119
- Caps, contraceptive, 413
- Capsorin*, 439
- Captopril, **100**
see also ACE inhibitors
- Carbagen SR*, 221
- Carbaglu*, 499
- Carbamazepine
 bipolar disorder, 181, **220**
 epilepsy, 219, **220**, 221
 neuropathic pain, 213
 palliative care, 16
 poisoning, elimination, 24
 trigeminal neuralgia, **220**
- Carbimazole, 373, **374**
- Carbocysteine, **164**
 cystic fibrosis, 164
- Carbo-Dome*, 576
- Carbomers, 536
- Carbomix*, 25
- Carbon monoxide poisoning, 31
- Carbonic anhydrase inhibitors
 diuresis, 81
 glaucoma, 533
- Carboplatin, **433**
- Carboxylase defects, 500
- Cardene* preparations, 105
- Cardiac arrest, 112, 470
- Cardiac glycosides, 72
- Cardiac *see also* Heart
- Cardiopulmonary
 arrest, 112
 resuscitation, 112
- Cardiopulmonary resuscitation
 chart, *inside back cover*
- Cardura* preparations, 97
- CareSens N* products, 370
- Carglumic acid, 498, 499
- Carmellose, **536**, 537
- Carmize*, 537
- Carnitine *see* Levocarnitine, **494**
- Carnitor*, 494
- Carobel*, *Instant*, 807
- Carteolol, **532**
- Carticaine *see* Articaine, **655**, 656
- Carvedilol, 86, **88**
see also Beta-adrenoceptor blocking drugs
- Cascara, 58
- Caspofungin, 304, 305, **310**, 311
- Castor oil, 58
- Catacrom*, 530
- Catapres*, 97
- Catheter maintenance, 417
- Catheter patency solutions
 chlorhexidine, 417
 sodium chloride, 418
 solution G, 418
 solution R, 418

Cautionary and advisory labels, 820

counselling, 820

NCL, 820

original packs, 820

recommended wording, *inside back cover*

Causton, 277

Ceanel Concentrate, 590

Cefaclor, **270**, 271

Cefadroxil, **270**, **271**

Cefalexin, 270, **271**

Cefixime, 270, **272**

Cefotaxime, 270, **272**

Cefpodoxime—*discontinued*

Cefradine, 270, **272**, 273

Ceftazidime, 270, **273**

eye drops, 536

Ceftriaxone, 270, **273**, 274

Haemophilus influenzae

prophylaxis, 258

meningococcal meningitis

prophylaxis, 258

Cefuroxime, 270, **274**, 275

eye drops, 536

Celevac, 57

CellCept, 437

Cellulitis, 257

Cellulisc, 537

Celsenti, 325

Central nervous system

stimulants, 188

Ceph... *see also* Cef...

Cephalosporins, 269

Ceporex, 271

Ceprotin (protein C concentrate), 123

Cepton, 600

Cerazette, 408

Cerebral oedema, 80, 377

Cerelle (desogestrel), 408

Cerezyme, 495

Cernevit, 474

Cerumol, 545

Cervarix, 616

Cetirizine, 152, **153**

Cetraben, 558, 561

Cetrimide

scalp, 590

skin, 563, 599, **601**

benzalkonium with, 563

chlorhexidine with, 601

dimeticone with, 563

CFCs, 145

Charcoal, activated, **24**, **25**

Charcodote, 25

Cheilitis, angular, 552, 565

Chenodeoxycholic acid, **68**

Chickenpox, 325, 631

corticosteroids, 377

Chilblains, 108, 603

Children, prescribing for, 1

Chirocaine, 656

Chlamydia

eye, 255, 524

genital, 253

macrolides, in, 283

Chloractil (chlorpromazine), 174

Chloral betaine *see* Cloral betaine, 169

Chloral hydrate, **169**

clinical procedures, 642

Chlorambucil, **424**, 425

Chloramphenicol

ear, 541, **543**

eye, 524, **525**

systemic, 287, **288**

ChloroPrep, 600

Chlorhexidine

bladder infections, 417

mouth, 549, 551, **553**

chlorobutanol with, 553

nose, neomycin with, 549

skin

benzalkonium with, 560

emollient with, 560

hydrocortisone and

nystatin with, 567

skin disinfection, 599, **600**,

601

cetrimide with, 601

dusting powder, 600

Chlorine poisoning, 32

Chlorobutanol, 553

Chlorofluorocarbon propellants, 145

Chloromycetin, 525

Chloroquine

malaria

prophylaxis, 336, 342, **343**

treatment, 335, **343**

proguanil with, 343

Chlorothiazide

chronic hypoglycaemia, 368

diabetes insipidus, 391

hypertension, **76**

Chloroxylonol, 602

Chlorphenamine, 152, **155**

allergic emergencies, 158

Chlorpheniramine *see*

Chlorphenamine

Chlorpromazine

nausea and vomiting, 192,

195

psychosis, **174**

Chlortalidone, **77**

Cholecalciferol *see* Colecalciferol

Cholera vaccine, **609**

travel, 632

Cholestasis, 68, 69

Cholestatic conditions, 68

Cholesterol, 69

Smith-Lemli-Opitz syndrome,

69

Cholestyramine *see* Colestyramine

Cholic acid, 68

Choline, 485

Choline salicylate dental gel, 550,

551

Cholinergic crises, 518

Cholinesterase inhibitors, 518, 651

Choragon, 388

Choreas, 241

Chorionic gonadotrophin, 384,

388

Chronic myeloid leukaemia, 434

Churg-Strauss syndrome, 150

Cicafem (co-cyprindiol), 584

Ciclesonide, **148**

Ciclosporin

aplastic anaemia, 454

eczema, 578, **579**

immunosuppression, 438, **439**

nephrotic syndrome, 439

psoriasis, 578, **579**

rheumatic disease, 513

ulcerative colitis, 47, 53, **54**

Cidofovir, 328

Cidomycin, 282

Cigarette smoking, 242

Cilastatin, 275

imipenem with, 275

Cilest, 406

Ciloxan, 526

Cinchocaine

[ingredient], 66

rectal, 65

Cinnarizine, **193**, 194

Cinryze, 161

Cipramil, 187

Ciprofloxacin, 301, **302**

Crohn's disease, 48

ear, 542, 544

eye, 524, **525**, 526

meningococcal meningitis

prophylaxis, 258

Ciproxin, 302

Circadin, 170

Cisatracurium, 648, **649**

Cisplatin, 433, **434**

Citalopram, 186, **187**

Citanest preparations, 659

Citramag, 64

Citrulline, 498, **499**

Clairette, 584

Clarithromycin, 284, **285**

Helicobacter pylori eradication,

41

pertussis prophylaxis, 258

Classification changes, xviii

Clasteon, 396

Clavulanic acid, 264

amoxicillin with, 264, 266

ticarcillin with, 268, **269**

Cleansers, skin, 599

Clenil Modulte, 146

Clexane preparations, 115

ClickSTAR, 363

Clindamycin, **287**

acne, 582

bacterial vaginosis, 400

benzoyl peroxide with, 581

malaria, 334, 335

oral infections, 287

pneumocystis pneumonia, 350

vaginal infections, 400

Clinitas, 538

Clinitek Microalbumin, 372

ClinOleic, 473

Clinutren Dessert, 787

Clioquinol

ear, 541, 543

skin

betamethasone with, 569

fluocinolone with, 570

- Clobazam, 234
epilepsy, 219, **235**
- Clobetasol propionate, 569
neomycin and nystatin with, 569
- Clobetasone butyrate, 569
tetracycline with, 569
- Clodronate sodium *see* Sodium clodronate, 396
- Clofarabine, **428**
- Clonazepam
epilepsy, 219, 234, **235**, 236
injection—*discontinued*
- Clonidine, **96**, 97
- Cloral betaine, 169
- Clostridium botulinum*, 609
- Clostridium difficile*, 48
antibacterial therapy, 249
metronidazole in, 299
vancomycin in, 289
- Clotrimazole
anogenital, 399
ear, 543
skin, 594, **595**
betamethasone with, 569
hydrocortisone with, 567
vulvovaginal candidiasis, recurrent, 399
- Clozapine, 171, 173, **178**, 179
- Clozaril, 178
- Cluster headache, 215
- CMV *see* Cytomegalovirus
- Coal tar, 572, 573
bath, 576
diethanol and salicylic acid with, 577
scalp, 576, 590, 591
skin, 576
zinc with, 576
- Co-amiflofruse, 80
- Co-amilozone, 80
- Co-amoxiclav, 264, **266**, 267, 268
- Cobalamin-H* (hydroxocobalamin), 453
- COC *see* Contraception, oral, combined
- Cocaine, poisoning by, 30
- Co-careldopa, 239, **240**
- Co-codamol preparations, 201, 202
- Cocis, 576
- Co-cyprindiol, **584**
- Cod liver oil, zinc oxide with, 563
- Co-danthramer preparations, 59
- Co-danthrusate preparations, 59
- Codeine
cough suppressant, 166
diarrhoea, 46
pain, 204, **205**, 206
bucizine and paracetamol with, 203
paracetamol with, 201, 202
palliative care, 16
morphine equivalence, 17
- Codipar preparations, 202
- Co-dydramol preparations, 202, 203
- Celiac disease, 475
ACBS, 808
- Co-enzyme Q10 *see* Ubidecarenone, **502**
- Co-fluampicil, 264, 266
- Colazide, 49
- Cold sores, 597
- Colecalciferol, 487, **489**
calcium with, 489, 490
- Colestid*, 127
- Colestipol, **127**
- Colestyramine
diarrhoea, 45, **69**
familial
hypercholesterolaemia, 69
hypercholesterolaemia, **127**
pruritus, 69
palliative care, 19
- Colic, bowel, palliative care, 19
- Colief, 807
- Colifoam, 53
- Colistimethate sodium, 291, **292**
eye drops, 536
- Colistin *see* Colistimethate sodium
- Colistin sulfomethate sodium *see* Colistimethate sodium
- Colitis
Clostridium difficile infection, 48
ulcerative, 47
- Collodion
definition, 557
flexible, 599
- Colloidal oatmeal, 558, 561
- Colobreathe, 292
- Colofac preparations, 39
- Colomycin, 292
- Colophony, 586, 599
- Colpermin, 40
- Coma
hyperglycaemic, 366
hyperosmolar nonketotic, 366
hypoglycaemic, 367
hypothyroid, 372
insulin, 366
ketoacidotic, 366
- Co-magaldrox, 36
- Combined hormonal contraceptives, 403
see also Contraception
- Combivir, 319
- Combun-3 Test, 372
- Compact, 370
- Companies, specialist-importing, 840
- Complan Shake, 788
- Complementary medicine, 2
- Compliance, 1
- Concerta XL, 191
- Concordance, 1
- Condylina, 587
- Condylomata acuminata, 587
- Confusion, palliative care, 19
- Congenital agammaglobulinaemia, replacement therapy, 628
- Conjunctivitis, 255, 524
allergic, 528
- Conotrane, 563
- Constipation, 56
palliative care, 18
- Contact lenses, 540
- Contiflo XL (tamsulosin), 415
- Continuous subcutaneous infusions, palliative care, 19
- Contour products, 370
- Contraception, 401
devices, 411, 412, 413
contraceptive caps, 413
contraceptive diaphragms, 413
implants, 409
intra-uterine system, 410, 411
oral, 401
combined hormonal, 401
emergency, 413, 414
missed pill, 402, 408
progestogen-only, 405
starting routines, 404, 408
surgery, **403**, 408
travel, 402
parenteral, **409**
spermicidal, 411
transdermal, 401, 405
detached patch, 402
starting routines, 403
- Controlled drugs, 8
travel abroad, 10
- Conversion tables, *inside back cover*
- Convulex, 233
- Convulsions
febrile, 239
palliative care, 18
poisoning and, 24
see also Epilepsy
- Convulsive status epilepticus, 236
- Co-phenotrope, 46
- Copper T 380A, 412
- Coracten preparations, 106
- Cordarone X, 84
- Cordilox preparations, 108
- Corn flour, ACBS, 812
- Corn starch, ACBS, 812
- Corneal ulcers, 524, 527
- Coronary heart disease
prevention
antiplatelet therapy, 118
diabetes, 91
dyslipidaemia, 124
hypertension, 90
non-drug treatment, 90
obesity, 90
risk assessment, 124
- Corrected gestational age, xiv
- Corsodyl preparations, 553
- Corticotropin, 387, **388**
- Corticosteroids, **375**
administration, 377
adrenal suppression, 377
allergic emergencies, 158
allergy, 377
nasal, 545, 546
anaesthesia, 377, 634
anaphylaxis, 377
angioedema, 377
aphthous ulcers, 549, **550**

Corticosteroids (*continued*)—

asthma, 144
 acute, severe, 132
 chronic, 133
 blood disorders, 454
 breast-feeding, 379
 cancer, 437
 chickenpox, 377
 croup, 135
 ear, 541
 equivalent doses, 376
 eye, 525, 527
 haemorrhoids, 65
 hepatic impairment, 379
 hypercalcaemia, 479
 immunosuppression, 437
 infantile spasms, 219
 infections, 377
 inflammatory bowel disease, 47, 52
 inhaled, 144
 measles, 377
 mouth, **550**
 myasthenia gravis, 518, 519
 nasal polyps, 545
 neuropathic pain, 213
 pregnancy, 379
 proctitis, 53
 proctosigmoiditis, 53
 psychiatric reactions, 378
 renal impairment, 379
 replacement therapy, 375
 rheumatic disease, 510
 septic shock, 376
 side-effects, 379
 skin
 choice, 565
 eczema, 564, 572
 nappy rash, 563
 potency, 566
 psoriasis, 565, 574
 steroid treatment card, 379
 surgery, 377, 634
 tuberculosis, 295
 ulcerative colitis, 52, 53
 withdrawal of, 378
 Corticotrophin *see* Corticotropin, 387
 Corticotrophin-releasing hormone *see* Corticorelin, 387, **388**
 Corticotropin, 387
 Cortisol, 375
 Co-simalcite [ingredient], 36
CosmoFer, 451
Cosopt, 534
Cosuric (allopurinol), 422
 Co-trimoxazole, 292, **293**
 pneumocystis pneumonia, 292, 293, 350
 Cough
 palliative care, 18
 suppressants, 166
 Coumarins, 116
 Covering creams, 589
Covermark preparations, 589
Cow & Gate Pepti preparations, 793
Cozaar preparations, 102

Crab lice, 598
 Cradle cap, 573, 590
 Creams
 definition, 557
 suitable quantities, 557
 Creatinine clearance *see* Glomerular filtration rate
 Creeping eruption *see* Cutaneous larva migrans, 354
Creon preparations, 70, 71
Crestor, 126
 Cretinism *see* Hypothyroidism, neonatal, 372
CRH Ferring, 388
 CRH *see* Corticorelin, 387, **388**
 Crisantaspase, **432**
 Crohn's disease, 47
 fistulating, 48
 Cromoglicate (*or* cromoglycate) *see* Sodium cromoglycate
 Crotamiton, 563, 564
 scabies, 597
 Croup, 135
 Cryptococcosis, 304
Crystacide, 602
Crystapen, 262
 CS gas *see* CS spray, 32
 CS spray, 32
Cuplex, 586
Curatoderm, 575
Curosurf, 162
Cu-Safe T300, 412
 Cushing's syndrome, 383, 396
 corticosteroid-induced, 379
 Cutaneous larva migrans, 354
Cutivate, 571
CX Antiseptic Dusting Powder, 600
 Cyanides, poisoning by, 31
 Cyanocobalamin, 452
Cyanokit, 31
Cyclimorph, 210
 Cyclizine
 motion sickness, 193
 nausea and vomiting, 193, **194**
 palliative care, 19
 Cyclopentolate, **530**
 Cyclophosphamide, **425**, 436
 Cycloplegics, 530
 Cycloserine, **296**, 297
 Cyclosporin *see* Ciclosporin
Cyklokaprone, 122
Cymevene, 329
 Cyproterone
 acne, 584
 precocious puberty, 385, **386**
Cystadane, 500
Cystagon, 497
 Cysteamine *see* Mercaptamine, **497**
 Cystic fibrosis
 delayed puberty, 383
 fat malabsorption, 69
 respiratory-tract infections, 251, 259, 268
Cysticide, 353
Cystine500, 814
 Cystinosis, nephropathic, 497
 Cystitis, 417
 haemorrhagic, 423
Cystrin, 416
 Cytarabine, **428**, 429
 Cytochrome oxidase deficiency, 485
 Cytokine modulators
 Crohn's disease, 54
 juvenile idiopathic arthritis, 514
 ulcerative colitis, 54
 Cytomegalovirus
 infections, 326, 328
 Cytotoxic drugs, 419
 alopecia, 421
 antibiotic, 426
 bone-marrow suppression, 421
 delayed toxicity, 421
 extravasation, 420
 handling guidelines, 419
 hyperuricaemia, 421
 nausea and vomiting, 420
 pregnancy, 421
 urothelial toxicity, 423

D

d4T *see* Stavudine, 314, **317**
 Dacarbazine, **432**
 Dactinomycin, **426**
Daktacort, 567
Daktarin
 oral gel, 552
 skin, 595
Dalacin, 287
 acne, 582
 bacterial vaginosis, 400
Dalivit, 492
 Dalteparin, **114**
 Danaparoid, **115**, 116
Dandrazol preparations, 590
 Dandruff, 590
Danlax, 59
 Danthron *see* Dantron, **58**
Dantrium, 521
 Intravenous, 654
 Dantrolene
 malignant hyperthermia, **654**
 muscle spasm, 520, **521**
 neuroleptic malignant syndrome, 173
 Dantron, **58**
 Dapsone
 pneumocystis pneumonia, 350, **351**
 poisoning, elimination, 24
Daraprim, 349
 Darbepoetin, **454**, 455
 Darier's disease, 574
 Darunavir, 314, **320**
 Daunorubicin, **426**, 427
DaunoXome, 427
DDAVP, 392
 DDI *see* Didanosine, **316**
 Decan, 474
Decapeptyl SR, 387

- Decongestants
nasal, 548
systemic, 167
- DEET *see* Diethyltoluamide, 336
- Defective medicines, 12
- Defenac* (diclofenac) preparations, 507
- Deferasirox, 457, **458**
- Deferiprone, 457, **458**
- Deferoxamine *see* Desferrioxamine
- Deflazacort, 376, **380**
- Deleted preparations, xviii
- Deltacortril* (prednisolone), 383
- Demeclocycline, **278**
- Demorem* (ondansetron), 198
- Demulcent cough preparations, 167
- Dendritic ulcer, 527
- Dental Practitioners' Formulary, 826
- Dental prescribing
abscess, 255
anaesthesia
general, 635
local, 655
vasoconstrictors, 655
angular cheilitis, 552
endocarditis prophylaxis, 260
fluoride, 482
herpes labialis, 325
herpetic gingivostomatitis, 325
infections
bacterial, 247, 255
fungal, 551
viral, 325, 551
joint prosthesis prophylaxis, 261
oral hygiene, 553
pain, 199, 205, 505
postoperative, 199
sedation, 642
sinusitis, 548
- Dentinex*, colic drops, 36
- Denzapine*, 179
- Dependence *see* Drug dependence
- DepoCyt*, 429
- Depolarising muscle relaxants *see* Muscle relaxants
- Depo-Medrone*, 382, 511
with *Lidocaine*, 511
- Depo-Provera*, 409, 410
- Depression, 183
antipsychotics, 171
manic, 181
- Derbac-M*, 598
- Dermablend*, 589
- Dermabond ProPen*, 599
- Dermacolor* preparations, 589
- Dermal*, 590
- Dermalo*, 561
- Dermamist*, 558
- Dermatitis
ACBS, 818
herpetiformis, 808
seborrhoeic, 572
see also Eczema
- Dermatological preparations, special-order, 556
- Dermatonic Once Heel Balm*, 560
- Dermatophyte infections, 305, 594
- Dermol* preparations, 560, 562
- Dermovate*, 569
- Desferal*, 459
- Desferrioxamine
aluminium overload, **458**
eye, 536
iron overload, 457, **458**, 459
iron poisoning, **29**
- Desflurane, **639**
- Desitrend* (levetiracetam), 226
- Desloratadine, 152, **153**
- Desloughing agents, 602
- Desmomelt*, 392
- Desmopressin, 392
assessment tests, **391**
diabetes insipidus, 390, **391**
fibrinolytic response, **391**
haemophilia, 121, **391**
nocturnal enuresis, **391**, 417
- Desmospray*, 392
- Desmotabs*, 392
- Desogestrel, 408
ethinylestradiol with, 406
- Destolit*, 68
- Detemir, insulin *see* Insulin
detemir, **361**
- Detrusitol* preparations, 416
- Dexamethasone, 376, **380**, 381
bacterial meningitis, 380
cerebral oedema, 380
corticosteroid replacement therapy, 381
croup, 135
inflammatory and allergic disorders, 380
ear, 542, 543
eye, 528
malignant disease, 437
nausea and vomiting, 193
palliative care
anorexia, 17
dysphagia, 18
dyspnoea, 18
nausea and vomiting, 19
neuropathic pain, 16
raised intracranial pressure, 19
suppression test, 377
- Dexamfetamine, 188, **189**
- Dexamphetamine *see* Dexamfetamine, 188, **189**
- Deximune*, 440
- Dexomon* (diclofenac) preparations, 507
- Dexsol* (dexamethasone), 381
- Dextrogel*, 367
- Dextromethorphan, 166
- Dextropropoxyphene, poisoning by, 27
- Dextrose monohydrate *see* Glucose
- DF 118 Forte*, 207
- DHC Continus*, 207
- Diabetes insipidus, 390
- Diabetes mellitus, 356
diagnosis, 372
genetic defects of beta-cell function, 355
- Diabetes mellitus (*continued*)—
management with insulin, 356
monitoring, 358
glucose, 369
ketone, 369
meters, 370, 371
test strips, 370, 371
neonatal, 359
surgery, 358
- Diabetic
ketoacidosis, 366, 469
nephropathy, 369
neuropathy, 369
- Diabur Test-5000*, 369
- Diacomit*, 229
- Dialamine*, 804
- Dialar* (diazepam), 521
- Diamicron*, 365
- Diamorphine, 204, **206**
palliative care, 17, 19
morphine equivalence, 17, 19
syringe drivers, 20
- Diamox* preparations, 534
- Dianette*, 584
- Diaphragms, contraceptive, 413
- Diarrhoea, 45
oral rehydration, 466
- Diastix*, 369
- Diazemuls* (diazepam), 237
- Diazepam
acute drug-induced dystonia, 241
convulsions, 24
epilepsy
status epilepticus, **236**, 237
muscle spasm, 520, 521
palliative care
anxiety, 17
convulsions, 18
dyspnoea, 18
muscle spasm, 18
tetanus, 521
- Diazepam Desitin*, 237
- Diazepam Rectubes*, 237
- Diazoxide
chronic hypoglycaemia, 368
hypoglycaemia, **368**
injection—*discontinued*
resistant hypertension, **92**
- Dibenylone*—*discontinued*
- Dibucaine *see* Cinchocaine
- Diclofenac
actinic keratoses, 589
eye, 540
eye surgery, 539
fever, **506**
juvenile idiopathic arthritis, 507
pain and inflammation, **506**, **507**
postoperative pain, 645
rheumatic disease, 505, 506, 507
- Diclofenac potassium, 506
- Diclofenac sodium, 507
- Dicloflex* (diclofenac) preparations, 507

- Diclomax* preparations, 507
Diclozip (diclofenac), 507
 Dicobalt edetate, 31
 Dicyclomine *see* Dicycloverine, **38**
 Dicycloverine, **38**
 Didanosine, **316**
 Dienogest, estradiol with, 407
Dietary Specials products, 808, 809, 810
 Diethylcarbamazine, 354
 Diethyltoluamide, 336
Differin, 583
Difflam
 oral rinse, 550
 spray, 550
Diffudox XL (tamsulosin), 415
Diffucan preparations, 306
 Diflucortolone valerate, 570
DigiFab, 74
 Digoxin, 72, **73**
 arrhythmias, 82
 poisoning, 73
 Digoxin-specific antibody fragments, 73, **74**
 Dihydroartemisinin *see* Artemisol, **344**
 Dihydrocodeine, 204, **206**, 207
 palliative care, morphine equivalence, 17
 paracetamol with, 202, 203
 Dihydropyridine calcium-channel blockers, 104
 Dihydrotestosterone, 487
 Dihydroxycholecalciferol, 487
 Diloxanide furoate, **347**
 Diltiazem, 104, **105**
 anal fissure, 67
 poisoning by, 29
 see also Calcium-channel blockers
 Dimercaprol, 31
 Dimeticone
 head lice, 597, **598**
 skin
 benzalkonium with, 563
 cetrimide with, 563
 zinc oxide with, 563
 Dinoprostone, **130**
Diocetyl, 59
 Dioctyl sodium sulphosuccinate *see* Docusate sodium
Dioderm, 566
Dioralyte preparations, 466
Diovan, 103
Dipentum, 51
Dipeptiven, 474
 Diphenoxylate, 46
 Diphenylbutylpiperidines, 171
 Diphosphonates *see* Bisphosphonates
 Diphtheria
 antibacterial
 prophylaxis, 258
 treatment, 261
 antitoxin, 611
 immunisation, 609
 travel, 610
 vaccines, combined, **610**, 611
 Dipotassium hydrogen phosphate, 481
Diprivan, 638
Diprobase, 558
Diprobath—discontinued
Diprosalic, 568
Diprosone, 568
 Dip/Ser, 611
 Dipyridamole, **119**
 Disease-modifying antirheumatic drugs, 512
 Disfiguring skin lesions, ACBS, 819
 Disinfectants, 599
 ACBS, 819
Diskhalar
 Becodisks—discontinued
 Relenza, 332
 Serevent—discontinued
 Disodium clodronate *see* Sodium clodronate, 396
 Disodium cromoglicate *see* Sodium cromoglicate
 Disodium folinate, 423
 Disodium hydrogen phosphate, 481
 Disodium levofolinate, 423
 Disodium pamidronate *see* Pamidronate disodium, **395**
Distaclor preparations, 271
 Distal intestinal obstruction syndrome
 acetylcysteine, 164
 amidotrizoates, 64
Distamine, 493
 Dithranol, 573, 574, **576**, 577
 coal tar and salicylic acid with, 577
Dithrocream, 577
Ditropan, 416
 Diuretics
 anaesthesia and, 635
 beta-blockers with, 86
 carbonic anhydrase inhibitors, 81
 loop, 75, 77
 osmotic, 80
 potassium and, 464
 potassium with, 81
 potassium-sparing, 75, 79
 with other diuretics, 80
 thiazides, 75
 DMARDs *see* Disease-modifying antirheumatic drugs, 512
 DMPS *see* Unithiol, 31
 DMSA *see* Succimer, 31
 Dobutamine, 108, **109**, 110
 infusion table (neonatal), 824
DocOmega, 814
 Docusate sodium
 ear, 545
 laxative, 58, **59**
Docusol, 59
Dolmatil, 177
Dolocodon PR, 211
 Dolutegravir, 314, **324**
 Domperidone
 migraine, 215
 Domperidone (*continued*)—
 nausea and vomiting, 192, **196**
 palliative care, 18
 Dopamine, 108, **110**
 infusion table (neonatal), 824
Dorisin XL (fluvastatin), 126
 Dornase alfa, 164, 165
Dorzant (dorzolamide), 534
 Dorzolamide, 533, **534**
 timolol with, 534
 Dose changes, xvii
 DOT (directly observed therapy), 295
Doublebase preparations, 558, 561
Dovobet preparations, 575
Dovonex, 575
Doxadura (doxazosin) preparations, 97
 Doxazosin, 97, 415
 cardiovascular, **97**
 urinary tract, **415**
 Doxepin
 oral, **185**
 topical, 563, **564**
 Doxorubicin, **426**, **427**
 Doxycycline, **278**, 279
 acne, 584
 aphthous ulcers, **550**, 551
 malaria prophylaxis, 336, **347**
 malaria treatment, 334, 335, 347
 mouth, 551
 oral infections, 278
 periodontitis, 255, **550**, 551
Doxylar (doxycycline), 279
Doxzogen XL (doxazosin), 97
Dozac, 175
Drapolene, 563
 Dravet syndrome, 219
 Dressings, pain on changing, 640
Driclor, 602
 Dried prothrombin complex, **122**
 Driving and skilled tasks, 2
 Droperidol, 192, **195**
Dropodex, 528
 Drosiprenone
 contraception
 ethinylestradiol with, 406
 Drug dependence, 205
 management, 242
 prescribing in, 8
 Drug information services, *inside front cover*
 Drug interactions, 660
 Dry mouth, 554
 palliative care, 18
Duac, 581
 Dual block, 651
 Ductus arteriosus, 129, 130
Dukoral, 609
Dulcolax (bisacodyl), 58
Dulcolax Pico (sodium picosulfate), 60
 Perles—discontinued
Duocal preparations, 802, 803
Duofilm, 586
Duphalac (lactulose), 61

Duraphat, 483
mouthwash—*discontinued*
Durogesic DTrans, 208
Dusting powders, 557
Dymista, 547
Dysentery
amoebic, 347
bacillary see *Shigellosis*, 248
Dysfunctional voiding, 415
Dysmenorrhoea, 199
Dyspepsia, 34
Dysphagia, palliative care, 18
Dyspnoea, palliative care, 18
Dysport, 242
Dystonias, 239
drug-induced, 241

E
E numbers, *inside back cover*
E45 preparations, 559, 561
Itch Relief, 560
EAA supplement, 815
Ear
infections, 541
wax removal, 544
EarCalm, 542
Easi-Breathe
Salamol, 138
Easiphen, 815
Easyhaler
beclomethasone, 146
budesonide, 147
formoterol, 136
salbutamol, 138
Ebetrex—*discontinued*
Ebufac (ibuprofen), 508
Echinocandin antifungals, 304, 310
Echinococcosis, 353
Econac (diclofenac), 507
Econazole
anogenital, 400
skin, 594, **595**
vaginal, 400
Ecopace (captopril), 100
Ecstasy
controlled drug, 8
liquid (sodium oxybate), 30
poisoning by, 30
Ectopic tachycardia, 81
Eculizumab, **459**
Eczema, 572
ACBS, 818
ear, 542
scalp, 590
Eczmol, 560
Ednyt (enalapril), 101
Edrophonium
anaesthesia, 651, **652**
myasthenia gravis, 518, **519**
Efavirenz, 314, **322**
emtricitabine and tenofovir
with, 318
Efcortisol, 382
Efomoterol see Formoterol
Elaprase, 496
Electrolade, 466

Electrolyte and water replacement
intravenous, 467
oral, 463
Electrolyte concentrations, 463
intravenous fluids, 463
Electrolytes
intravenous nutrition, 474
Element products, 370
Elemental-028 Extra, 774
Elidel, 580
ellaOne, 414
Elocon, 571
Elspar, 432
Eltroxin (levothyroxine), 373
Eludril preparations, 553
Elvanse, 190
Emadine, 529
Emedastine, 528, **529**
Emerade, 160
Emergencies in the community,
medical, *inside back cover*
Emergency
contraception, 413
supply, medication, 7
Emeside, 222
EMLA, 658
Emollients, 558
eczema, 572
pruritus, 563
palliative care, 19
psoriasis, 573
Emollin, 559
Emozul, 44
Emsogen, 779
Emtricitabine, 314, **316**
efavirenz and tenofovir with,
318
tenofovir with, 318
Emtriva, 316
Emulsiderm, 562
Emulsifying ointment, 558
Emustil, 538
Enalapril, **100**, 101
see also ACE inhibitors
Enbrel, 517
Enbucrilate, 599
Encephalopathy, hepatic, 61
En-De-Kay preparations, 482, 483
Endocarditis, 249, 250, 280
antibacterial prophylaxis, 260
Endophthalmitis, 524
Ener-G products
gluten- and wheat-free, 810
gluten-free, 808, 809
low-protein, 810, 811
Energivit, 803
Energy, intravenous nutrition, 473
Enfamil preparations, 794
thickened, 797
Enfuvirtide, 314, **324**
Engerix B, 615
Enkephalinase inhibitors, 47
Enoxaparin, 114, **115**
Enoximone, **74**
Enshake, 805
Ensure Plus preparations, 784, 785,
787
Ensure preparations, 778, 783
Entamoeba histolytica, 347
Entecavir, 329
Enteral
feeding tubes
administering drugs via,
67
clearing blockages, 67
nutrition, 475
foods, ACBS, 771
Enteric infections, 248
Enterobiasis, 352
Enterocolitis, necrotising, 249
Entocort preparations, 52
Entonox, 640
Enuresis, nocturnal, 416
Enzira, 617
Enzyme induction, 660
Enzymes, fibrinolytic, 120
Epaderm preparations, 559
Epanutin preparations, 228
capsules—*discontinued*
Ready Mixed Parenteral, 239
Epaxal, 613
Ephedrine
hypotension, **110**, 111
nasal congestion, **548**
Epiduo, 583
Epiglottitis, 250
Epiglu, 599
Epilepsy, 216
breast-feeding and, 218
driving, 218
neonatal seizures, 219
pregnancy and, 218
status epilepticus, 236
non-convulsive, 236
syndromes, 219
Epilim preparations, 232, 233
Epinastine, 528, **529**
Epinephrine see Adrenaline
EpiPen preparations, 160
Epirubicin, 426, **427**
Episenta preparations, 232, 233
Epival, 233
Epirivir, 317
Epoetin
alfa, **455**
beta, **455**, 456
zeta, **455**, 456
Epoprostenol, 93, **94**, 95, 116
infusion table (neonatal), 824
Eposin, 431
Eprex, 455
Eptacog alfa (activated), 122
Eptadone (methadone), 208
Equanox, 640
Equasym XL, 191
Ergocalciferol, 487, **488**
Ergot alkaloids, 213
Ertapenem, **275**
Erwinase, 432
Erymax, 286
Erysipelas, 257
Erythema, perianal, 65
Erythrocine, 286
Erythromycin, 284, **286**
acne, 582, 583, 584
tretinoin with, 583

- Erythromycin (*continued*)—
 diphtheria prophylaxis, 258
 eye infections, 525
 gastro-intestinal stasis, 40
 pneumococcal prophylaxis, 259
 rheumatic fever prophylaxis, 258
- Erythroped preparations, 286
- Erythropoietins, 454
- Eslicarbazepine, 219
- Esmeron, 650
- Esmolol, 81, 86, **89**
see also Beta-adrenoceptor blocking drugs
- Esomeprazole, **43**, 44
- Essential amino acids supplement, 815
- Estradiol
 contraception
 dienogest with, 407
- Estriol, labial adhesions, 398
- Etanercept
 juvenile idiopathic arthritis, 514, **516**, 517
 psoriasis, **580**
- Ethambutol, 294, 296, **297**
 tuberculosis treatment, 295
- Ethanol, poisoning, use in, 31
- Ethinylestradiol
 acne *see* Co-cyprindiol, **584**
 contraception, 401
 desogestrel with, 406
 drospirenone with, 406
 etonogestrel with, 405
 gestodene with, 406, 407
 levonorgestrel with, 406, 407
 norelgestromin with, 405
 norethisterone with, 406, 407
 norgestimate with, 406
 hormone therapy, **383**, 384
- Ethinylestradiol *see*
 Ethinylestradiol
- Ethosuximide, 219, **222**
- Ethyl-2-cyanoacrylate, 599
- Ethylene glycol, poisoning by, 31
- Etomidate, **636**
- Etomidate-Lipuro, 636
- Etonogestrel
 ethinylestradiol with, 405
 implant, 409, 410
- Etopophos, 431
- Etoposide, **431**
- Etoricoxib, 505, **508**
- Etravirine, 314, **323**
- Etretinate, 574
- Eucalyptus oil, 166
- Eucerin, 560
- Eudemine, 368
 injection—*discontinued*
- Eumovate, 569
- Euratesim, 344
- Eurax preparations, 564
- European viper venom antiserum, 33
- Everolimus, **434**
- Evohaler
 Flixotide, 148
 Seretide, 149
 Serevent, 139
 Ventolin, 138
- Evolutra, 428
- Evra, 405
- Excipients
 details provided, 2
 skin preparations and, 557
- Exfoliative dermatitis, 376
- Exjade, 458
- Exocin, 526
- Exorex, 576
- Expectorants, 167
- Extemporaneous preparations, 6
- Exterol, 545
- Extrapyramidal symptoms
 antipsychotics and, 172, 173
 treatment, 241
- Extravasation, 522
- Eye
 anaesthesia, local, 535
 antibacterials, 524
 frequency of administration, 525
 antifungals, 527
 antivirals, 527
 contact lenses, 540
 corticosteroids, 527
 cycloplegics, 530
 drops, administration, 523
 glaucoma, 531
 inflammation, 527
 lotions, administration, 524
 microbial contamination, 524
 miotics, 535
 mydriatics, 530
 ointments, administration, 523
 prostaglandins, 531, 532
- Ezetimibe, **128**
 simvastatin with, 127
- Ezetrol, 128
- F**
- Fabrazyme, 495
- Fabry's disease, 495
- Factor VIIa (recombinant), 122
- Factor VIII fraction, 122
 inhibitor bypassing, 123
- Factor IX fraction, 123
- Factor XIII fraction, 123
- Faecal softeners, 60
- Falciparum malaria, 334
- Fallot's tetralogy *see* Tetralogy of Fallot, 87
- Famciclovir, 326, 400
- Familial hypercholesterolaemia, 123
- Fanhdii (factor VIII fraction), 122
- Fansidar, 346
- Fasigyn, 348
- Fasturtec, 422
- Fat emulsions, intravenous, 474
- Fate products, 811
- Faverin, 188
- Favism, 460
- Febrile convulsions, 239
- Fectrim (co-trimoxazole), 293
- Feed thickeners, 477, 807
- Feeds *see* Foods
- FEIBA (factor VIII inhibitor bypassing fraction), 123
- Feldene preparations, 510
- Felypressin, 655
 prilocaine with, 659
- FemCap, 413
- Femidom, 401
- Femodene preparations, 406
- Femodette, 406
- Femulen—*discontinued*
- Fenactol (diclofenac) preparations, 507
- Fenbid—*discontinued*
- Fencino (fentanyl), 208
- Fendrix, 615
- Fenofibrate, **128**
- Fentalis (fentanyl), 208
- Fentanyl, 204, **207**, 208
 analgesia
 peri-operative, 645, **646**
 assisted ventilation, **646**
 palliative care, 16
 morphine equivalence, 17
 transdermal route, 17
- Fentazin, 176
- Fenticonazole, 400
- Ferinject, 451
- Ferric carboxymaltose, 450, **451**
- Ferriprox preparations, 458
- Ferrous fumarate, **449**, 450
- Ferrous gluconate, 449, 450
- Ferrous sulfate, **449**
- Fersaday, 449
- Fersamal—*discontinued*
- Feverfen (ibuprofen), 508
- Hexofenadine, 152, **153**
- Fibrates, 128
- Fibrinogen, dried, **123**
- Fibrinolytic drugs, 120
- Fibrogammin P (factor XIII fraction), 123
- Filariasis, 354
- Filaricides, 354
- Filgrastim, **461**, 462
- Filnarine SR, 210
- Finacea, 582
- Finax products, 809
- Fingertip unit, 566
- Fits *see* Epilepsy
- Flagyl preparations, 300
- Flamatak (diclofenac) preparations, 507
- Flamazine, 593
- Flamrase (diclofenac) preparations, 507
- Flavour Mix, 807
- Flavouring preparations, 807
- FlavourPac, 807
- Flebogamma DIF, 630
- Flecainide, 81, 82, **84**, 85
- Fleet Ready-to-use enema, 63
- Flexbumin preparations (albumin), 471
- Flexible collodion, 599
- Flexi-T intra-uterine devices, 412

Flexitol Heel Balm, 560
Flexotard MR (diclofenac), 507
Flixonase preparations, 547
Flixotide preparations, 148
Flofan, 95
Flomaxtra XL, 415
Florinef, 376
Flowfusor, 600
Floxapen (flucloxacillin), 264
Flu-Amp (co-fluampicil), 266
Fluarix, 617
Fluarix Tetra, 617
Fluclomix (flucloxacillin), 264
Flucloxacillin, **263**, 264
 ampicillin with [co-fluampicil], 264
 ear infection, 542
Fluconazole, 304, **305**, 306
 oropharyngeal candidiasis, 551
 palliative care, 18
 vulvovaginal candidiasis, recurrent, 399
Flucytosine, 304, 311, **312**
Fludara, 429
Fludarabine, 428, **429**
Fludrocortisone, 375, **376**
Fludroxycortide, **570**
Fluenz, 617
 Fluid and electrolyte replacement, 463
 neonate, 468
 oral, 463
 parenteral, 467
Flumazenil, 29, **553**
Flumetasone, **543**
Flumethasone *see* *Flumetasone*, **543**
Flunisolide—*discontinued*
Fluocinolone acetonide, 570
 clioquinol with, 570
 neomycin with, 571
Fluocinonide, 571
Fluocortolone, 571
 [ingredient], 66
Fluor-a-day, 483
Fluorescein, **539**
 lidocaine with, 535
 proxymetacaine with, 536
Fluoride, **482**, 483
FluoriGard mouthwash, 483
Fluorometholone, 528
Fluorouracil, 589
Fluoxetine, 186, **187**
Flurandrenolone *see* *Fludroxycortide*, **570**
Flurbiprofen
 eye, 540
 sore throat, 550, 551
Fluticasone
 asthma, 144, **148**
 formoterol with, 148
 salmeterol with, 149
 vilanterol with, 149
Fluticasone furoate
 nasal allergy, 547
Fluticasone propionate
 asthma
 chronic, 133

Fluticasone propionate
 (continued)—
 nasal allergy, **546**, 547
 azelastine with, 547
 nasal polyps, 547
 skin, 571
Flutiform, 148
Fluvastatin, 124, **125**
Fluvirin, 617
Fluvoxamine, 186, **187**, 188
FML, 528
 Focal seizures, 219
 Folate deficiency, 452
 Folate rescue, 422
 Folic acid, **453**, 454
 anaemias, 452
 methotrexate, following, 513
 pregnancy, 452
 Folinic acid, **422**
 rescue, 422
 Folliculitis, 591
 Fomepizole, 31
 Food allergy, 56
Foodlink preparations, 788
 Foods
 ACBS, **771**
 enteral, 475
 feed thickeners, 477
 gluten-free, 808
 intolerance, 476, 807
 low-protein, 810
 special diets, 474, 476, 808
 vitamin supplements, 492
 thickened, 807
Foradil, 136
Forceval, 492
Forceval Junior capsules—
 discontinued
 Formaldehyde, 586
Formoterol, **136**
 budesonide with, 147
 fluticasone with, 148
 Formulary
 Dental, 826
 Nurse, 828
Forticare, 797
Forticreme, 788
Fortijuice, 784
Fortimel Regular, 787
Fortini preparations, 779, 781
Fortipine LA 40, 106
Fortisip preparations, 785, 786, 788
Fortum, 273
Fosamax preparations, 395
Fosamprenavir, 314, **320**
Foscarnet, 328, **329**
Foscavir, 329
Fosphenytoin, 228, **237**
Fragmin, 114
Framycetin, **543**
 ear, 543
 eye, 528
 Frangula, sterculia with, 58
Frebini preparations, 779, 781, 782
FreeStyle products, 370
 Fresh frozen plasma, 123

Fresubin preparations
 enteral feed, 772, 774, 775, 776
 soya formula, 773
 feed supplement, 802
 nutritional supplement, 784, 786, 789
 Friars' Balsam, 166
Frisium (clobazam), 235
 Fructose
 ACBS, 807
 fructose-based infant formula, 796
 presence of, 2
FruitiVits, 806
Frumil preparations (co-amilofruse), 80
Frusemide *see* *Furosemide*
Frusol (furosemide), 78
 FTC *see* *Emtricitabine*
 FTU *see* *Fingertip unit*, 566
Fucibet, 569
Fucidin, 288
 skin, 593
Fucidin H, 567
Fucithalmic, 526
Fulsovin—*discontinued*
Fultium-D₃, 489
 Fungal infections, 304
 anogenital, 398
 eye, 527
 oral, 304
 oropharyngeal, 551
 skin, 305, 594
 Fungating tumour, palliative care, 18
Fungizone, 310
Furadantin—*discontinued*
Furosemide, 77, **78**
 amiloride with, 80
Fusidic acid
 angular cheilitis, 552
 eye, 524, 526
 skin, **593**
 betamethasone with, 569
 hydrocortisone with, 567
 systemic, 288
Fuzeon, 324
Fybogel, 57
Fybogel Mebeverine, 40
Fycompa, 226

G
 G6PD deficiency
 drugs to be avoided in, 460, 461
GA gel, 811
GA1 Anamix, 811
Gabapentin, 219, **222**, 223
Gabitril, 230
Galactomin preparations, 794, 796
Galenamox (amoxicillin), 265
Galenphol, 166, 167
Galfex, 450
Galpseud, 167
Galsulfase, **496**
Gammagard S/D, 630

Gamma-hydroxybutyrate (sodium oxybate), 9, 30
Gammanorm, 629
Gammalex, 630
Gamunex, 630
 Ganciclovir, **328**, 329
Gardasil, 616
 Gas-gangrene
 prophylaxis, 260
 treatment, 261
 Gastric emptying, poisoning and, 25
Gastrocote, 37
 Gastro-enteritis, 45, 248
Gastrografin, 65
 Gastro-intestinal procedures, antibacterial prophylaxis, 259
 Gastro-intestinal secretions
 electrolyte content, 463
 Gastro-oesophageal reflux disease, 34
 Gaucher's disease, 495
Gaviscon preparations, 37
 G-CSF *see* Granulocyte-colony stimulating factor, 461, 462
Gedarel preparations, 406
 Gelatin
 infusion, 471, **472**
 succinylated, 472
Gelofusine, 472
Geloplasma, 472
 Gels, definition, 557
GelTears, 536
Generaid preparations, 797, 798
 General anaesthesia *see* Anaesthesia, general
 Genetic defects of beta-cell function, 355
 Genital warts, 587
Genius products, 808
Genotropin preparations, 389
 Gentamicin, 280, **281**, 282
 ear, 543, 544
 eye, 524, 526, 536
Genticin, 282
 ear, 544
 eye, 526
Gentisone HC, 543
 German measles *see* Rubella
 Gestational age *see* Corrected gestational age, xiv
 Gestodene, ethinylestradiol with, 406, 407
 GHB (sodium oxybate), 9, 30
Giardia lamblia, 348
 Giardiasis, 348
 Gilles de la Tourette syndrome *see* Tourette syndrome, 241
 Gingivitis
 antibacterial treatment, 255, 299
 mouthwashes, 553
Glamin, 473
Glandosane, 554
 Glargine, insulin *see* Insulin glargine, **361**
 Glaucoma, 531
 steroid, 527
 Glibenclamide, 364, **365**

Gliclazide, **365**
Glivec, 435
 Glomerular filtration rate, dosage and, 13
Glucagen HypoKit, 368
 Glucagon, **367**, 368
 beta-blocker poisoning, 29
 Glucocorticoids
 equivalent doses, 376
 replacement therapy, 375
Glucodock products, 370
Glucogel, 367
Glucolab products, 370
Glucomen products, 370, 371
Glucophage, 366
Glucorx products, 371
 Glucose
 ACBS, 807
 cyanosis, 87
 hypoglycaemia, 367
 infusion, 469
 potassium and, 470
 sodium and, 468
 intravenous nutrition, 473
 oral rehydration, 466
 presence of, 2
 syrup, hydrogenated, presence of, 3
 tests
 blood, 369
 tolerance, 372
 urine, 369
 Glucose 6-phosphate dehydrogenase deficiency
 drugs to be avoided in, 460, 461
Glucotrend, 371
 Glue ear, 544
 Glulisine, insulin *see* Insulin glulisine, 359, **360**
Glutafin products
 gluten- and wheat-free, 810
 gluten-free, 808, 809, 810
 Glutaraldehyde, 586
 Glutaric
 acidaemias, 485
 aciduria, 811, 812
Glutarol, 586
 Gluten, presence of, 3
 Gluten-free foods, ACBS, 808, 809, 810
 Gluten-sensitive enteropathies, 808
 Glycerin suppositories, 60
 Glycerol
 constipation, 58, **59**
 Glyceryl trinitrate
 anal fissure, 67
 extravasation, 522
 infusion table (neonatal), 825
 shock, 109
 vasodilation, **103**
 Glycogen storage disease
 dietary supplement, 812
 granulocyte-colony stimulating factor, in, 461
 hypoglycaemia, 367
 Glycopeptide antibiotics, 288
Glycophos, 474

Glycopyrrolate *see* Glycopyrronium bromide
 Glycopyrronium bromide
 airway secretions, 641
 hyperhidrosis, 602
 hypersalivation, **641**
 neuromuscular blockade reversal
 neostigmine with, 652
 palliative care, 18, 19
 premedication, 640, **641**, 642
Glycosade, 812
Glypressin, 393
 GnRH *see* Gonadorelin, **390**
 Goitre, lymphadenoid, 372
 Gold, 512
Golden Eye preparations, 527
 Gonadorelin, **390**
 Gonadorelin analogues, 385
 Gonadotrophin deficiency, 383
 Gonadotrophin-releasing hormone
 see Gonadorelin, **390**
 Gonadotrophins, 388
Gonapeptyl, 387
 Gonorrhoea
 antibacterial treatment
 eye, 255
 genital, 253
 pharyngeal, 253
GoQuick, 389
 GORD *see* Gastro-oesophageal reflux disease, 34
 Goserelin, **386**
 Gout, 518
 Gramicidin
 ear, 543
 eye, 528
 Granisetron, 193, **197**
Granocyte, 463
 Granulocyte-colony stimulating factor, 461, 462
 Grass pollen extracts, 156, 157
 Graves' disease, 374
Grazax, 157
 Griseofulvin, 305, 311, **312**
 Ground-nut oil *see* Arachis oil
 Growth hormone, 388
GSF-Syrup, 367
 Guillain-Barré syndrome, 628
Gygel, 411
 Gynaecological surgery, antibacterial prophylaxis, 260
GyneFix, 411, 412
Gynest, 398
Gyno-Daktarin Ovule, 400
Gyno-Pevaryl preparations, 400
Gynoxin preparations, 400

H
Haelan preparations, 570
 Haem arginate, **502**
Haemate P (factor VIII fraction), 122
Haemoctin (factor VIII fraction), 122
 Haemodialysis, 25
 Haemolytic anaemia, 454
 G6PD deficiency, 460

- Haemonine* (factor IX fraction), 123
- Haemophilia, 391
- blood products, 122, 123
- Haemophilus influenzae* type b (Hib)
- immunisation, **611**, 612
 - prophylaxis, 258
 - vaccines
 - diphtheria with, 610
 - meningococcal with, 612
- Haemorrhage, 121
- gastro-intestinal, 41
- Haemorrhagic disease of newborn, 491
- Haemorrhoids, 65
- Haemostatics, 121
- HAES-steril*, 472
- Haldol*, 175
- tablets—*discontinued*
- Haleraid*, 143
- Half-Beta-Proprane* (propranolol), 88
- Half-Inderal LA*—*discontinued*
- Half-Securon SR*, 108
- HaloLite*, 95
- Haloperidol
- movement disorders, 241
 - nausea and vomiting, **174**, 192
 - palliative care, 18, 19
 - psychosis, **174**, 175
 - tics, **174**
- Harifen* products, 810
- Harlequin ichthyosis, 578
- Hartmann's solution *see* Sodium lactate, intravenous infusion, compound, 468, 469
- Hashimoto's thyroiditis, 372
- Havrix* preparations, 613
- Hay fever, 152, 545
- Hay-Crom* preparations (sodium cromoglicate), 530
- HBIG *see* Hepatitis B immunoglobulin, **630**, 631
- HBvaxPRO*, 615
- HCG *see* Chorionic gonadotrophin, 384, **388**
- HCU* preparations, 812
- Head lice, 597
- Headache
- cluster, 215
 - migraine, 213
- Heaf test, 609
- Healthy Start* vitamins, 485
- Heart *see also* Cardiac
- Heart failure, 75
- ACE inhibitors, 75
 - beta-blockers, 75, 86
 - diuretics, 75, 77
 - enoximone, 75
 - spironolactone, 75
- Hedrin*, 598
- Helicobacter pylori*
- dyspepsia, 34
 - eradication, **40**
 - test, 40, 41
- Helixate NexGen* (factor VIII fraction), 123
- Helminth infections, 352
- Hemohe*s, 472
- Heparin, **113**
- flushes, 116
 - infusion table (neonatal), 825
 - injection
 - calcium, 114
 - sodium, 114
- Heparinoids, topical, 603
- Heparon Junior*, 798
- Hepatect*, 631
- Hepatic
- encephalopathy, 61
 - impairment, prescribing in, 13
- Hepatitis A
- immunisation, 612
 - immunoglobulin, normal, 628
 - travel, 632
 - vaccine, **612**, 613
 - hepatitis B with, 613
 - typhoid with, 614
- Hepatitis B
- auto immune, 377
 - chronic, 317, 329
 - chronic active, 445
 - immunisation, 614
 - immunoglobulin, **630**, 631
 - travel, 632
 - vaccine, **614**, 615
- Hepatitis C
- chronic, 329
 - chronic active, 445
- Hepatolenticular degeneration *see* Wilson's disease, 493
- Hepatryx*, 614
- Herbal medicines, 2
- surgery, 635
- Hereditary angioedema *see* Angioedema, 160
- Heroin *see* Diamorphine
- Heron* products
- gluten- and wheat-free, 810
 - gluten-free, 809
- Herpes infections, 325
- eye, 527
 - genital, 326, 400
 - immunoglobulin, 631, 632
 - mouth, 551
 - skin, 596
- Hexetidine, 553
- HFAs, 145
- HGH *see* Somatotrophin, 389
- Hib *see* *Haemophilus influenzae* type b
- Hibi* liquid, 600
- Hibiscrub*, 600
- Hibitane* preparations, 600, 601
- Hiccup, 174
- palliative care, 18
- Hidrasec*, 47
- Hirsutism, 584
- Hirudoid*, 603
- Histamine H₁-antagonists, 151
- Histamine H₂-antagonists, 41
- Histoacryl*, 599
- Histoplasmosis, 305
- HIV infection
- pregnancy, 313
 - treatment, 313
- Hizentra*, 629
- HNIG *see* Immunoglobulins, normal, 628, **629**, 630
- Hodgkin's disease, 432
- Homatropine, **530**
- Homocystinuria, 500, 812
- Hookworm infections, 353
- Hormone replacement, 383
- androgens, 384
 - oestrogens, 383
 - progestogens, 383
- How to use BNFC, xi
- HPV *see* Human papillomavirus, vaccine, 615, **616**
- HRF* *see* Gonadorelin, **390**
- 5HT₁-receptor agonists, 213
- 5HT₃-receptor antagonists, 193, 197, 421
- HTIG *see* Immunoglobulins, tetanus, 631
- Humalog* preparations, 360, 363
- Human chorionic gonadotrophin *see* Chorionic gonadotrophin, 384, **388**
- Human coagulation factor VIII, 122
- Human factor VIII fraction, 122
- Human factor IX fraction, 123
- Human factor XIII fraction, 123
- Human fibrinogen *see* Fibrinogen, dried, **123**
- Human papillomavirus, vaccine, 615, **616**
- HumaPen Luxura* products, 363
- HumaPen Memoir*, 364
- Humatrope, 389
- Humira, 516
- Humulin I*, 362
- Humulin M3*, 363
- Humulin S*, 359
- Hyabak*, 538
- Hyaline membrane disease, 162
- Hydatid disease, 353
- Hydralazine, 91, **92**
- Hydrex*, 600
- Hydrochlorothiazide, amiloride with, 80
- Hydrocortisone, 376, 377, **381**, 382
- asthma, acute, 132
 - colitis, 53
 - ear, 543
 - eye—*discontinued*
 - haemorrhoids, 65, 66
 - intra-articular, 511
 - mouth, 550
 - pneumocystis pneumonia, 350
 - rectal, 65, 66
 - replacement therapy, 375
 - rheumatic disease, 511
 - septic shock, 109
 - skin, 566, 567
 - chlorhexidine and nystatin with, 567
 - clotrimazole with, 567
 - fusidic acid with, 567

Hydrocortisone
skin (*continued*)—
miconazole with, 567
nystatin with, 567
urea and lactic acid with,
567
urea with, 567
Hydrocortistab, 511
Hydrofluoroalkane propellants,
145
Hydrogen peroxide
mouthwash, 553, **554**
skin, **601**, 602
Hydromol preparations, 559, 561
HC Intensive—discontinued
Intensive, 560
Hydromoor, 537
Hydromorphone, **208**
palliative care, 16
morphine equivalence, 17
Hydrotalcite, **36**
simeticone with, 36
Hydrous ointment, 558
Hydroxocobalamin
anaemias, 452, **453**
cyanide poisoning, **31**
Hydroxycarbamide, **457**
sickle-cell disease, 456
Hydroxychloroquine, **512**, 513
Hydroxycholecalciferol, 487
Hydroxyethyl starch *see* Starch,
etherified, 471, 472
Hydroxyethylcellulose, 537
Hydroxyquinoline, benzoyl
peroxide with, 581
Hydroxyurea *see*
Hydroxycarbamide
Hydroxyzine, **155**
Hygroton, 77
Hylol preparations, 538
Hyoscine butylbromide, **38**, 39
palliative care, 19
Hyoscine hydrobromide
excessive respiratory
secretions, 198
hypersalivation, 198
motion sickness, 193
nausea and vomiting, **198**
palliative care
excessive respiratory
secretions, 18, 19
gastro-intestinal pain, 18
premedication, 640, **642**
HYPER LYS preparations, 813
Hyperactivity, attention deficit,
188
Hyperammonaemia, 498
Hypercalcaemia, 393, 394, 479
Hypercalciuria, 479
Hypercholesterolaemia, 123, 124,
127, 128
Hyperemesis gravidarum, 193
Hyperglycaemia, 356
antipsychotics and, 173
coma, 366
neonatal, 358
HyperHAES—discontinued
Hyperhidrosis, 602
Hypericum perforatum, 184

Hyperinsulinaemic
hypoglycaemia, 368
Hyperinsulinism, 367
Hyperkalaemia, **464**
see also Salbutamol, 137
Hyperlipidaemia, 123
Hyperlysinaemia, 813
Hypermethioninaemia, 812
Hypernatraemia, 468
Hyperosmolar hyperglycaemic
nonketotic coma *see*
Hyperosmolar hyperglycaemic
state, 366
Hyperosmolar hyperglycaemic
state, 366
Hyperphosphataemia, 481
Hyperprolactinaemia, 383
antipsychotics and, 172
Hypersalivation, 640
Hypersecretion, airways, 640
Hypersensitivity *see* Allergy
Hypertension, 90
ACE inhibitors, 99
beta-blockers, 86
crisis, 91
diabetes, 91
diuretics, 75, 77
malignant, 91
nephritis, 91
poisoning and, 23
portal, variceal bleeding in,
391
pregnancy, 91
pulmonary, 93, 116
renal disease, 91
thiazide diuretics, 75
Hyperthermia
malignant, 654
poisoning and, 24
Hyperthyroidism *see*
Thyrotoxicosis
Hypertonic sodium chloride, 165
Hyperuricaemia, 421
Hypnomidate, 636
Hypnotics, 168
Hypnovel, 644
Hypocalcaemia, 477
Hypodermic equipment, insulin,
363
Hypodermoclysis, 467
Hypogammaglobulinaemia, 628
Hypoglycaemia, 358
acute, 367
chronic, 368
hyperinsulinaemia, 368
neonatal, 367
Hypoglycaemic drugs, oral *see*
Antidiabetic drugs, oral, 364
Hypogonadism, 383, 384, 388
Hypokalaemia
diuretics and, 75
intravenous potassium, 469
potassium, oral, 464
Hypomagnesaemia, 479
Hyponatraemia
neonate, 468
sodium replacement
oral, 465
parenteral, 468

Hypophosphataemia, 480
Hypopituitarism, 375, 384
Hyposensitisation, 156
Hypotension, poisoning and, 23
Hypothalamic hormones, 390
Hypothermia
antipsychotics and, 173
poisoning and, 24
Hypothyroidism, 372
neonatal, 372
Hypovase, 98
Hypovolaemia, 471
Hypoxaemia, 162
Hypromellose, 537
Hypurin Isophane, 362
biphasic, 363
Hypurin Lente, 361
Hypurin Neutral, 359
Hypurin Protamine Zinc, 362

I
iBGStar, 371
Ibuprofen
ductus arteriosus, **129**
juvenile idiopathic arthritis,
508
migraine, 213
pain, 505, **508**
postoperative, 645
pyrexia, 508
post-immunisation, 605
rheumatic disease, 505, 508
Ichthammol, 572, **573**
zinc with, 573
Ichthyosis, 558, 574, 578
Idiopathic thrombocytopenic
purpura *see* Thrombocytopenic
purpura
Idursulfase, **496**
Ifosfamide, **425**
Ilaris, 446
Ilaxten, 153
Iloprost
pulmonary hypertension, 94,
95
Raynaud's syndrome, **108**
Ilube, 536
Imatinib, 434, **435**
IME-DC products, 371
Imidazole antifungal drugs, 309
Imiglucerase, **495**
Imigran preparations, 214
Imipenem, **275**, 276
Imipramine
attention deficit hyperactivity
disorder, 185
nocturnal enuresis, **185**, 186,
417
Imiquimod, **587**
Immukin, 446
Immune interferon *see* Interferon,
gamma-1b, **446**
Immunisation
immunity
active, 604
passive, 607
international travel, 632
schedule, 606

- Immunodeficiency, syndrome, acquired, 313
- Immunoglobulins, **627**
- aplastic anaemia, 454
 - hepatitis B, 630, 631
 - Kawasaki disease, 628
 - myasthenia gravis, 518
 - normal, 628, **629**, 630
 - passive immunity, 607, 627
 - rabies, **631**
 - tetanus, 631
 - thrombocytopenic purpura, 460
 - varicella–zoster, 631, 632
- Immunostimulants, 444
- Immunosuppressants
- malignant disease, 437
 - myasthenia gravis, 519
 - skin disease, 578
 - transplant rejection, 435
- Imodium* preparations, 46, 47
- Impetigo, 591
- systemic treatment, 257
 - topical treatment, 256
- Implanon*, 409
- Imuran*, 437
- Imuvac*, 617
- INCI synonyms, sunscreens, 588
- Increlex*, 397
- Independent prescribing, 830
- Inderal-LA*—discontinued
- Indian hemp *see* Cannabis
- Indinavir, 314
- Indolar SR* (indometacin), 509
- Indometacin
- ductus arteriosus, **129**
 - juvenile idiopathic arthritis, 509
 - pain and inflammation, 509
 - rheumatic disease, 505, **509**
- I-Neb AAD*, 95
- Inegy*, 127
- Infacol*, 36
- Infanrix-IPV*, 610
- Infantile
- acne, 580, 585
 - spasms, 219
- Infasoy*, 796
- Infatrin* preparations, 779, 793
- Infections
- amoebic, 347
 - antisera, 607, 627
 - ear, 541
 - eye, 524
 - fungal, 304
 - helminth, 352
 - immunoglobulins, 627
 - nail, fungal, 305
 - notifiable diseases, 246
 - oropharyngeal, 551
 - bacterial, 247, 255
 - protozoal, 334
 - skin, 591
 - trichomonal, 348
 - vaccines, 604
 - vaginal, 398
 - viral, 313
 - vulval, 398
- Inflammatory bowel disease, 47
- Inflexal V*, 617
- Infliximab
- Crohn's disease, 47, 54, **55**
 - inflammatory bowel disease, 48
 - rheumatic diseases, 514
 - ulcerative colitis, 47, 54, **55**
- Influenza
- immunisation, **617**
 - prophylaxis, 330
 - treatment, 330
 - vaccines, 616
 - seasonal, 617
- Influvac Desu*, 617
- Information services
- medicines, *inside front cover*
 - poisons, 23
- Infusions, intravenous (neonatal), 823
- Inhalations
- aromatic, 166
 - Benzoin tincture, compound, 166
 - menthol and eucalyptus, 166
 - steam, 548
- Inhaler devices, 142
- Injex*, 364
- Innohep*, 115
- Innovace*, 101
- Inositol, 485
- Inotropic drugs, positive, 72, 108
- Inovelon*, 229
- Insect stings, 33, 152, 563, 564
- Insecticides, poisoning by, 32
- Insomnia, 168
- antihistamines, 152
 - palliative care, 18
- Instillagel*, 657
- Insulet*, 364
- Insulatard* preparations, 362
- Insulin, 356
- aspart, 359, **360**
 - biphasic, 361, **362**
 - detemir, **361**
 - glargine, **361**
 - glulisine, 359, **360**
 - human, 356
 - infusion
 - intravenous, 357, 358
 - subcutaneous, 357
 - infusion table (neonatal), 825
 - injection equipment, 363, 364
 - isophane, 361, **362**
 - biphasic, 361, **363**
 - lispro, 359, **360**
 - biphasic, 361, **362**, 363
 - protamine zinc, 361, **362**
 - soluble, **359**
 - zinc suspension, **361**
 - crystalline, 361
 - mixed, 361
- Insulin-like growth factor, 397
- Insuman*
- Basal, **362**
 - Comb *preparations*, 363
 - Rapid, **359**
- Intal*, 150
- Intelence*, 323
- Interactions, 660
- Interferon
- alfa, 444, 445
 - chronic hepatitis B, 329
 - chronic hepatitis C, 330
 - peginterferon, 329, 330
 - gamma-1b, **446**
 - peginterferon alfa, 445
- Interferon gamma release assay, 609
- International nomenclature, cosmetic ingredients *see* INCI synonyms, 588
- International travel, immunisation for, 632
- Intracranial pressure, raised
- corticosteroids, 377
 - osmotic diuretics, 80
 - palliative care, 19
- Intralipid* preparations, 473
- local anaesthetic toxicity, 655
- Intratec*, 630
- Intra-uterine devices
- copper-bearing, 411, 412, 413
 - progestogen-releasing, 410, 411
- Intravenous
- infusion table (neonatal), 824
 - infusions, 467
 - nutrition, 472
- IntronA*, 445
- Invanz, 275
- Iodide, 374
- Iodine
- radioactive, 374
 - skin disinfection, **601**
 - thyrotoxicosis, 373, 374
- Iopidine*, 539
- Ipolcol*, 50
- Ipratropium
- asthma, 139, **140**
 - acute, 132
 - rhinorrhoea, **548**, 549
 - Steri-Neb*, 140
- IPV *see* Poliomyelitis, immunisation, 623
- Iron
- deficiency, 448
 - neonatal, 449
 - oral, 448, 449, 450
 - overload, 457
 - parenteral, 450, 451, 452
 - poisoning by, 29
- Iron dextran, 450, **451**
- Iron sucrose, 450, **451**, 452
- Ironorm*, 449
- Irriclen*, 600
- Iripod*, 600
- Irritable bowel syndrome, 37, **48**
- Istentress* preparations, 325
- Isoflurane, **639**
- Isogel*, 57
- Issoleucine50*, 815
- Isoniazid, 296, **297**
- tuberculosis prophylaxis, 259
 - tuberculosis treatment, 294, 295

Isophane protamine insulin *see*
Insulin, isophane
Isoplex, 472

Isoprenaline, 109

Isopto

Alkaline, 537

Plain, 537

Isotretinoin, 580

acne

erythromycin with, 583

oral, 584, **585**, 586

topical, 582, **583**

Isotrex, 583

Isotrexin, 583

Isovaleric acidaemia, 813

Isovorin, 423

Ispagel Orange, 57

Ispaghula

constipation, **57**

diarrhoea, 45

mebeverine with, 40

Istin, 105

Itraconazole, 304, 305, **306**, 308

oropharyngeal candidiasis,
551

IUDs *see* Intra-uterine devices

IVA Anamix preparations, 813

Ivacaftor, **165**

Ivermectin

larva migrans, 354

onchocerciasis, 354

scabies, 597

strongyloidiasis, 354

Ixiaro, 618

IZS *see* Insulin, zinc suspension

J
Japanese encephalitis
immunisation, 618
vaccine, **618**

Jet nebulisers, 144

Jevity preparations, 772, 775, 776

Jext preparations, 160

Joy-Rides, 199

Juvela products

gluten-free, 808, 809, 810

low-protein, 810, 811

K
Kala-azar, 348
Kalcipos-D, 490
Kaletra, 321
Kalydeco, 165
Kaolin, 45
Kapake preparations, 202
Kaplon (captopril), 100
Katya 30/75, 406
Kawasaki disease
aspirin, 119
dipyridamole, 119
immunoglobulin, 119
Kay-Cee-L, 464
Kefadim, 273
Keflex, 271
Keftid (cefaclor), 271
Kemadrin preparations, 241

Kemeticine, 288

Kenalog Intra-articular/
Intramuscular, 512

Keppra, 226

Keratitis, 524

Keratoconjunctivitis, vernal, 528

Keratolytics, warts and calluses,
586

Keratosis follicularis, 574

Keromask preparations, 589

Ketalar, 637

Ketamine

abuse, 9

anaesthesia, **636**

clinical procedures, 642

palliative care, 16

sedation, **636**

Ketoacidosis, diabetic, 366

KetoCal preparations, 798, 799

Ketoconazole, 309

scalp, 590

skin, 594

tablets—*discontinued*

Ketodiastix, 372

Ketones

monitoring

blood, 369, 370, 371

urine, 369, 372

Ketorolac

eye, 540

pain, postoperative, **645**

Ketostix, 369

Ketotifen

eye, 528, **529**

systemic, **155**

Ketovite, 492

KeyOmega, 815

Kindergen, 799

Kiovig, 630

Kivexa, 315

Klaricid preparations, 285, 286

Klean-Prep, 63

Klinefelter's syndrome, 383

Kogenate Bayer (factor VIII
fraction), 123

Kolanticon, 38

Konakion preparations, 492

Kuvan, 475

Kwells, 199

Kytril, 197

L
Labelling, cautionary and advisory
see Cautionary and advisory
labels

Labeltalol, **86**, **89**

see also Beta-adrenoceptor
blocking drugs

Labial adhesions, 398

Labour, analgesia, 204

Labyrinthine disorders, 193

Lacosamide, 219, **223**, 224

Lacri-Lube, 537

Lactase, ACBS, 807

Lactate *see* Sodium lactate,
compound, 468, 469

Lactic acid

hydrocortisone and urea with,
567

salicylic acid with, 586

urea with, 560

vaginal infections, 400

Lactic acidosis, 315

congenital, 485

Lactose, presence of, 3

Lactugal (lactulose), 61

Lactulose, **61**

Ladropen (flucloxacillin), 264

Laevolac (lactulose), 61

Laevulose *see* Fructose

Lamictal, 225

Lamisil

oral, 313

topical, 596

Lamivudine, **317**

abacavir and zidovudine with,
316

abacavir with, 315

chronic hepatitis B, 317, 329

HIV infection, 314

zidovudine with, 319

Lamotrigine, 219, **224**, 225

Landau-Kleffner syndrome, 219

Lanolin, excipient, 559

Lanoxin preparations, 74

Lansoprazole, 43, **44**

Lantus preparations, 361

Lanvis, 430

Largactil, 174

Lariam, 344

Laronidase, **496**, 497

Larvae, sterile, 602

Laryngojet, 657

Lasix, 78

Lassa fever, 332

Lassar's paste, 577

Latanoprost, **532**

Latin abbreviations, *inside back*
cover

Laxatives, 56

bulk-forming, 57

faecal softeners, 60

osmotic, 61

palliative care, 18

stimulant, 58

Laxido Orange, 61

Legionnaires' disease, 283

Leishmaniasis, 348

Lennox-Gastaut syndrome, 219

Lenograstim, 461, **462**, 463

Leptospirosis, 261, 277

Lescol preparations, 125, 126

Leucine100, 815

Leukeran, 425

Leukotriene receptor antagonists,
150

Leuporelin, **386**, 387

Levamisole, **353**

Levemir preparations, 361

Levest, 406

Levetiracetam, 219, **225**, 226

Levobunolol, **532**

Levobupivacaine, **656**

Levocarnitine, **494**

Levocetirizine, 152, **153**, 154
 Levodopa
 dopa-decarboxylase inhibitor with, 239
 dystonias, 239
 metabolic disorders, 240
 Levofloxacin, eye, 524, **526**
 Levofolinic acid, **423**
 Levomepromazine, **175**
 nausea and vomiting, 192
 palliative care, 19
Levonelle 1500, 414
Levonelle One Step, 414
 Levonorgestrel, 410
 contraception, 409
 emergency, 413, **414**
 ethinylestradiol with, 406, 407
 intra-uterine, 411
 menstrual disorders, 384
 Levothyroxine, **372**, 373
Lexpec (folic acid), 454
 LH-RH *see* Gonadorelin, **390**
 Lice, 597, 598
 Licensed medicines, 2, 6
 Lidocaine
 arrhythmias, 82, **85**, 86
 eye, **535**
 fluorescein with, 535
 local anaesthesia, 655, **657**, 658
 catheterisation, 417
 dental, 655, 657
 phenylephrine with, 658
 prilocaine with, 657, 658
 urethral pain, 417
 neonatal seizures, 219
 rectal, 66
 ventricular fibrillation, 81
 ventricular tachycardia, 81
 Life support
 newborn, 112
 paediatric, 112
Lifestyle products, 808
 Lignocaine *see* Lidocaine
Lignospan Special, 657
Li-Liquid, 183
 Linezolid, **290**, 291
Lioresal, 520
 Liothyronine, 372, **373**
Lipantil, 129
 Lipid emulsion, local anaesthetic toxicity, **655**
 Lipid-regulating drugs, 123
Lipistart, 795
Lipitor, 125
Lipobase, 559
 Lipodystrophy syndrome, 314
Lipofundin preparations, 473
Liposic—discontinued
Lipostat, 126
LiquiBand, 599
 Liquid and White Soft Paraffin Ointment, 558
 Liquid paraffin, eye ointment, **537**, 538
Liquifilm Tears, 538
Liquigen, 802
Liquivisc, 536

Lisdexamfetamine, 188, **189**, 190
 Lisinopril, **101**
 see also ACE inhibitors
Liskonum, 183
 Lispro, insulin *see* Insulin lispro
 Lithium
 bipolar disorder, 181
 mania, 181
 poisoning by, 29
 surgery, 635
 Lithium carbonate, **182**, 183
 Lithium citrate, **183**
 Liver *see* Hepatic
Livwell products, 808
LMX 4, 657
Loa loa, 354
Load 375, 412
 Local anaesthetics *see* Anaesthesia, local
Locasol, 796
Loceryl, 595
Locoid preparations, 567
Locorten-Vioform, 543
 Lodoxamide, 528, **529**
Loestrin preparations, 406
Logynon preparations, 407
Lomotil (co-phenotrope), 46
Longtec, 211
Loniten, 93
 Loperamide
 diarrhoea, **46**
 simeticone with, 47
 palliative care, 18
Lophlex preparations, 815, 817
 Lopinavir, 314, **320**
 ritonavir with, 321
Lopresor preparations, 90
Loprofin products, 810, 811
 PKU drink, 815
Sno-Pro, 815
 Loratadine, 152, **154**
 Lorazepam
 convulsions, 24
 palliative care
 anxiety, 17
 dyspnoea, 18
 premedication, **643**
 status epilepticus, 236, **237**
Loron, 396
 Losartan, 101, **102**
Losac, 45
Losinate MR (tamsulosin), 415
 Lotions
 definition, 557
 eye, 524
 suitable quantities, 557
Lotriderm, 569
 Low-protein foods, ACBS, 810, 811
Lp-drink, 815
LPL 63.4, 561
 LSD *see* Lysergide
L-Tyrosine, 817
Lubristil preparations, 538
 Lugol's solution *see* Aqueous iodine oral solution, 374
Lumecare preparations, 536, 537, 538

Lumefantrine
 artemether with, **342**
 Lupus erythematosus, systemic, 377, 513
Lustral, 188
Luvinsta XL (fluvastatin), 126
Lyclear, 599
Lyflex (baclofen), 520
 Lyme disease, 264
 Lymecycline, **279**
 acne, 584
 Lymphogranuloma venereum, 277
Lyrinel XL, 416
 Lysergic acid diethylamide *see* Lysergide
 Lysergide, regulations, 9
Lysodren, 433
 Lysosomal storage disorder, 495, 496
M
Maalox preparations, 36
Mabron (tramadol), 212
MabThera, 444
Macrobid, 304
Macrodrantin, 304
 Macrogols, 61
 bowel cleansing, **63**
 constipation, **61**, 62
 faecal impaction, **61**, 62
 tear deficiency, **537**
 Macrolides, 283
 Maggots, 602
Magnapen, 266
Magnaspartate, 480
 Magnesium citrate, **64**
 sodium picosulfate with, **64**
 Magnesium glycerophosphate, **480**
 Magnesium hydroxide
 antacid, 36
 simeticone with, 36
 constipation, 62
 preparations, 62
 Magnesium salts
 constipation, 62
 Magnesium sulfate
 arrhythmias, 479
 asthma, 132
 hypocalcaemia neonatal, **479**
 hypomagnesaemia, **479**, 480
 pulmonary hypertension, 93, **95**
 torsade de pointes, **479**
 Magnesium trisilicate, **36**
 Magnesium-L-aspartate, **480**
 Malabsorption syndromes, 490
 electrolytes, 463
 vitamin K, 491
 Malaria
 falciparum, 334
 prophylaxis, 335, 337
 treatment, 334, 335
Malarivon, 343
Malarone, **346**
 malaria prophylaxis, 336, 345
 malaria treatment, 334, 345
 Paediatric, 346

- Malathion, 597, **598**
 Malignant disease, 419
 pain, 204
 bone, 200
 Malignant hyperthermia, 654
 Maltitol, 3
Mandelol, 537
Manevac, 60
 Mania, 171, 181
 Manic depression *see* Bipolar disorder, 181
 Mannitol
 diuresis, **80**, 81
 glaucoma, 531
 presence of, 3
 Mantoux test, 608
 Manufacturers
 index of, 831
 special-order, 840
 Maple syrup urine disease, 485, 813
 Maraviroc, 314, **324**, 325
Marcain preparations, 656
Marevan (warfarin), 118
 Marine stings, 33
 Marketing authorisation, 2
Marol (tramadol), 212
Martapan (dexamethasone), 381
Marvelon, 406
Matrifen (fentanyl), 208
 Maturity-onset diabetes of the young *see* Genetic defects of beta-cell function, 355
Maxidex, 528
Maxijul Super Soluble, 801
Maxitram SR (tramadol), 212
Maxitrol, 528
Maxolon preparations, 197
Maxtrex (methotrexate), 514
 McCune-Albright syndrome, 385
 MCT Oil, 802
MCT Peptide preparations, 795
 MDMA *see* Methylendioxy-methamphetamine
 Measles
 corticosteroids, 377
 immunisation, 618
 immunoglobulin, normal, 628
 vaccines, combined, 618, 619
 Measles, mumps and rubella vaccine, **619**
 Mebendazole, **352**, 353
 hookworm infections, 353
 roundworm infections, 353
 threadworm infections, 352
 whipworm infections, 352
 Mebeverine, **39**
 ispaghula with, 40
 Mecasermin, **397**
 Mecillinam, 269
 Meconium
 aspiration syndrome, 162
 ileus, uncomplicated, 47
 amidotriazoates, 64
Medac, 432
Medi, 142
Medicaid, 563
 Medical emergencies in the community, *inside back cover*
 Medicated bandages, 573
 Medicines information services, *inside front cover*
 Medicines, unlicensed, 2, 6
Medikinet preparations, 190, 191
Medi-Test products, 369, 372
Medocodene (co-codamol 30/500), 202
Medrone, 382
 Medroxyprogesterone, 409, 410
 Mefenamic acid, **509**
 dysmenorrhoea, 509
 menorrhagia, 509
 pain, 505
 rheumatic disease, 505
 Mefloquine
 malaria
 prophylaxis, 336, **343**
 treatment, 334, 343
 Megaloblastic anaemia, 452
 Meglumine amidotriazoate, 65
 Melatonin, **170**
Melophthal, 537
 Meloxicam, 505, **509**
 Melphalan, **425**
 Menadiol sodium phosphate, **491**
 Mendelson's syndrome, 41, 635
Mendor Discreet products, 371
Meningitec—discontinued
 Meningitis
 antibacterial therapy, initial, 251
 bacterial
 dexamethasone in, 380
 cryptococcal, 304
 fungal, 304
 haemophilus, 252
 listerial, 252
 meningococcal, 252
 prophylaxis, 258
 travel, 620, 632
 vaccine, 619, **620**, 621
 vaccine, Hib with, 612
 pneumococcal, 252
 streptococcal, 252
 Meningococcal *see* Meningitis
Menitorix, 612
Menjugate Kit, 620
 Menorrhagia, 410, 411
 antifibrinolytics, 121
 Menstruation
 postponement of, 384
 Menthol, eucalyptus with, 166
Menveo, 620
 Mepacrine, 512
Mepact, 447
 Meperidine *see* Pethidine, 204, 205, **212**
 Mepivacaine, 655, **658**
 Mercaptamine (cysteamine), **497**
 Mercaptopurine
 Crohn's disease, 53, **54**
 inflammatory bowel disease, 47, 48
 malignant disease, 428, **429**
 ulcerative colitis, 53, **54**
 6-Mercaptopurine *see* Mercaptopurine
Mercilon, 406
Meronem, 276
 Meropenem, 275, **276**
 Mesalazine, 47, **49**, 50
 Mesna
 cystic fibrosis, 164
 urothelial toxicity, **423**, 424
Mesren MR—discontinued
Mestinon, 519
 Mestranol, norethisterone with, 406
 Metabolic acidosis, 470
 Metals, poisoning by, 31
Metanium, 563
 Metaraminol, **111**
 Metformin, **366**
 Methadone
 neonatal abstinence syndrome, 242
 oral solution, 208
 pain, 204, **208**
 palliative care, 16
 poisoning by, 28
 Methaemoglobinaemia, 24
 Methanol, poisoning by, 31
Metharose (methadone), 208
 Methicillin-resistant *Staphylococcus aureus* *see* MRSA
 Methotrexate
 Crohn's disease, 47, 53, **54**
 folic acid with, 513
 malignant disease, 428, **429**, 430
 psoriasis, 578, **579**
 rheumatic disease, 512, **513**, 514
 Methotrimeprazine *see* Levomepromazine
 Methyl alcohol *see* Methanol
 Methyl salicylate, 600
 dithranol and salicylic acid with, 577
 Methyl salicylate [ingredient], 576
 Methylated spirit, industrial, 600
 Methylcellulose, **57**
 diarrhoea, 45
 Methylidopa, 96
 Methylene blue *see* Methylthioninium chloride, **24**
 Methylendioxy-methamphetamine controlled drug, 8
 poisoning by, 30
 Methylmalonic acidemia, 814
 Methylphenidate, 188, **190**, 191
 Methylprednisolone, **382**
 intra-articular, 511
 lidocaine with, 511
 rheumatic disease, 511
 Methylthioninium chloride, **24**
 Meticillin-resistant *Staphylococcus aureus* *see* MRSA
 Metoclopramide
 nausea and vomiting, 192, 193, **196**, 197, 421
 palliative care, 18
Metoject, 514
 Metolazone, 76, **77**
Metopirone, 397

- Metoprolol, 86, **89**, 90
 see also Beta-adrenoceptor blocking drugs
- Metosyn, 571
- Metogel, 593
- Metrolil, 301
- Metronidazole, **299**, 300, 301
 amoebiasis, 347
 bacterial vaginosis, 400
 Crohn's disease, 48
 giardiasis, 348
Helicobacter pylori eradication, 41
 oral infections, 299
 protozoal infections, 347
 rosacea, 581
 skin infections, 591, **593**, 594
 fungating tumours, 18
 trichomoniasis, 348
 vaginal, 400
- Metrosla, 593
- Metyrapone, 396, **397**
- Mezolar (fentanyl), 208
- Miacalcin, 394
- Micafungin, 305, 310, **311**
- Micanol, 577
- Micolette *Micro-enema*, 63
- Miconazole
 mouth, 551, **552**
 palliative care, 18
 skin, 594, **595**
 hydrocortisone with, 567
 vaginal, 400
- Micralax *Micro-enema*, 63
- Micral-Test II, 372
- Microalbustik, 372
- Microdot products, 371
- Microgynon preparations, 406
- Micronor, 409
- MicroPeak, 142
- Microphallus, 384
- Micropirin (aspirin), 119
- Midazolam
 anaesthesia, **643**, 644
 clinical procedures, 642, **643**
 convulsions, 24
 infusion table (neonatal), 825
 neonatal seizures, 219
 palliative care, 17
 convulsions, 18, 19
 dyspnoea, 18
 restlessness and confusion, 19
 premedication, 642, **643**
 status epilepticus, 236, **238**
- Mifamurtide, 446, **447**
- Miglustat, 495, **501**
- Migraine
 acute attack, 213
 beta-blockers, 87
 prophylaxis, 215
- Migraleve, 203
- Mildison, 566
- Milex diaphragms, 413
- Millinette preparations, 406
- Milrinone, **74**, 75
- Milupa
 Low Protein drink, 815
 PKU preparations, 815, 816
- Mineralocorticoids, 375
 replacement therapy, 375
- Mini TT 380 *Slimline*, 412
- Minijet
 Adrenaline, 159
 Atropine Sulfate, 641
 Furosemide, 78
 Glucose, 469
 Lidocaine, 86
 Magnesium Sulfate, 480
 Morphine Sulfate, 210
 Naloxone, 28
 Sodium Bicarbonate, 470
- Minims
 Artificial Tears, 537
 Atropine Sulfate, 530
 Chloramphenicol, 525
 Cyclopentolate, 530
 Dexamethasone, 528
 Fluorescein Sodium, 539
 Lidocaine and Fluorescein, 535
 Oxybuprocaine, 535
 Phenylephrine, 531
 Pilocarpine Nitrate, 535
 Prednisolone, 528
 Proxymetacaine, 536
 Proxymetacaine and Fluorescein, 536
 Saline, 538
 Tetracaine, 536
 Tropicamide, 531
- MiniQuick, 389
- Miniversol, 600
- Mini-Wright, 142
- Minocin MR, 279
- Minocycline, 277, **279**
 acne, 584
- Minoxidil, **92**, 93
- Miochol-E, 539
- Miphtel, 539
- Mirena, 410, 411
- Mission products, 369, 372
- Mistabron, 164
- Misuse of drugs
 Act, 8
 Regulations 2001, 8
- Mitochondrial disorders, 500
- Mitotane, **433**
- Mitoxantrone, 426, **427**
- Mitozantrone see Mitoxantrone, 426, **427**
- Mivacron, 649
- Mivacurium, 648, **649**
- Mizolastine, 152, **154**
- Mizollen, 154
- MMA/PA Anamix preparations, 814
- MMR vaccine, 618, 619
- MMRVaxPRO, 619
- Mobile, 370
- Modigraf, 442
- Modjul Flavour System, 807
- Modrasone, 568
- Modulen IBD, 799
- Moduret 25 (co-amiloride), 80
- MODY see Genetic defects of beta-cell function, 355
- Molaxole, 61
- Molcer, 545
- Mometasone
 asthma, 144, **149**, 150
 chronic, 133
 nasal allergy, **547**
 skin, **571**
- Monoamine-oxidase inhibitors, 186
- Monofluorophosphate, 482
- Monogen, 795
- Mononine (factor IX fraction), 123
- Montelukast, 150, **151**
- Morhulin, 563
- Morotocog alfa, 123
- Morphine
 infusion table (neonatal), 825
 neonatal abstinence syndrome, 242
 pain, 204, 205, **208**, 209, 210
 cyclozine with, 210
 palliative care, 16, 17
 breakthrough pain, 16
 buprenorphine equivalence, 17
 codeine equivalence, 17
 cough, 18
 diamorphine equivalence, 17, 19
 dihydrocodeine equivalence, 17
 fentanyl equivalence, 17
 hydromorphone equivalence, 17
 morphine equivalence, 17
 oxycodone equivalence, 17
 tramadol equivalence, 17
- Motifene, 507
- Motilium, 196
 suppositories—*discontinued*
- Motion sickness, 193
- Mouth ulceration, 549
- Mouthwashes, 553
- Movicol preparations, 61, 62
- Moxifloxacin, eye, 524, **526**
- Moxvigil, 526
- Mrs Crimbles products, 809
- MRSA, 263
 linezolid in, 290
 nasal, 549
- MST Continus, 210
- MSUD preparations, 813, 814
- MucoClear preparations, 165
- Mucodyne, 165
- Mucogel, 36
- Mucolytics, 164
 eye, 536
- Mucopolysaccharidosis, 496
- Mucosal bleeding, palliative care, 18
- Mucositis
 methotrexate-induced, 422
 oral, 420
- Multiload IUDs, 412
- Multiple myeloma, 454
- Multi-Safe devices, 412, 413

Multi-thick, 807
 Multivitamins, **492**
 Mumps

vaccines, **621**
 combined, 618, 619

Mupirocin

nose, 549
 skin, 591, **592**

Muscle relaxants

anaesthesia, 647
 depolarising, 651
 non-depolarising, 647
 skeletal, 520

Muscle spasm, 520

palliative care, 18

Musculoskeletal disorders,
 rheumatic, 504

MXL, 210

Myasthenia gravis

anticholinesterases, 518
 corticosteroids, 519
 diagnosis, 518
 diagnostic test, 519
 immunosuppressants, 519

Mycamine, 311

Mycifor XL (clarithromycin), 286

Mycobacterium avium complex
 infections, 295, 298

Mycobutin, 298

Mycophenolate mofetil, 436, **437**
 eczema, 578

Mycoplasma infections, 277

Mycota, 596

Mydiacyl, 531

Mydiatics, 530

Mydrilate, 530

MyGlucoHealth products, 371

Myleran, 424

Myoclonic seizures, 219

Myozyme, 498

Mysoline—discontinued

Myxoedema, juvenile, 372

N

Nabilone, 193, **198**

Nacrez (desogestrel), 408

Naglazyme, 496

Naims products, 808

Nalcrom, 56

Nalidixic acid, 301, **302**, 303

Naloxone

opioid poisoning, 27, **28**
 palliative care, 18
 postoperative, **653**

Nappy rash, 563

Naprosyn preparations, 510

Naproxen

dysmenorrhoea, 509
 juvenile idiopathic arthritis,
 509
 pain and inflammation, 505,
509, 510
 rheumatic disease, 505, 509

Narcolepsy, 188

Narcotic analgesics *see* Analgesics,
 opioid

Narcotic antagonists *see* Opioid
 antagonists

Naropin, 659

Nasacort, 547

Nasal

allergy, 545
 congestion, 545
 decongestants
 systemic, 167
 topical, 548

MRSA, 549

polyps, 545

Naseptin, 549

Nasobec preparations, 546

Nasofan, 547

Nasogastric feeding tubes *see*
 Enteral feeding tubes

Nasonex, 547

Natecal D3, 490

Nateglinide, 366

National Institute for Health and
 Care Excellence, 3

Nausea

cytotoxic drugs, 420
 motion sickness, 193
 opioid-induced, 193
 palliative care, 18
 postoperative, 193
 pregnancy, 193
 vomiting and, 192

Nebulisers, 143

Nebusal, 165

Necatoriasis, 353

Necrotising enterocolitis, 249

Nedocromil

asthma, **150**
 eye, 528, **529**

Neimann-Pick type C disease, 500

NeisVac-C, 620

Nelarabine, 428, **430**

Neocate preparations, 791, 792

Neoclarityn, 153

Neo-Cytamen (hydroxocobalamin),
 453

Neokay, 491

Neo-Mercazole—discontinued

Neomycin, 280

ear, 541, **544**
 betamethasone with, 542
 dexamethasone with, 542
 eye, 528
 betamethasone with, 528
 nose, 549
 chlorhexidine with, 549
 skin, 591, **592**
 betamethasone valerate
 with, 569
 clobetasol and nystatin
 with, 569
 fluocinolone acetoneide
 with, 571

Neo-NaClex preparations, 76

Neonatal

abstinence syndrome, 242
 seizures, 219

Neoral, 440

NeoRecormon, 456

Neo-Safe T380, 413

Neostigmine

myasthenia gravis, **518**, 519

Neostigmine (*continued*)—
 neuromuscular blockade
 reversal, **652**

glycopyrronium bromide
 with, 652

Neotigason, 578

Neuvent (salmeterol), 139

Nephropathic cystinosis, 497

Nephrotic syndrome

chlorthalidone, **424**

chlortalidone, **77**

ciclosporin, **439**

corticosteroids, 377

levamisole, **353**

spironolactone, **79**

Nepro, 799

Nerisone preparations, 570

Nerve agent, poisoning by, 32

Nesidioblastosis, 368

Neupogen, 462

Neural tube defects, prevention, 452

Neuralgia, postherpetic, 213

Neuroleptic malignant syndrome,
 173

Neuroleptics *see* Antipsychotics

Neuromuscular

blocking drugs, 647
 disorders, 518

Neurontin, 223

Neuropathic pain, 213

Neuropathy

compression, 511
 diabetic, 369

Neutral insulin *see* Insulin, soluble,
359

Neutropenias, 454, 461

Nevirapine, 314, **323**, 324

New names, xviii

New preparations, xviii

Nexium, 44

Nexplanon, 409, 410

NHS Direct, *inside front cover*

Nicam, 584

Nicardipine, 104, **105**

see also Calcium-channel
 blockers

NicAssist preparations (nicotine
 replacement therapy), 244, 245

NICE *see* National Institute for
 Health and Care Excellence, 3

Nicef (cefradine), 273

Niclosamide, 353

Nicorette preparations, 244

Nicotinamide, topical, 583, 584

Nicotine, **244**

replacement therapy, 243, 244

Nicotinell preparations, 245

Nifedipine, **105**, 108

angina, 104

chronic hypoglycaemia, 368

hypertension, 104

pulmonary hypertension, 93

Raynaud's syndrome, 104

see also Calcium-channel
 blockers

Nifedipress MR, 106

Niferex, 450

Nimbex, 649

Nimenrix, 620

- Nimodipine, 104, **107**
Nimotop, 107
Niquitin preparations, 245
 Nitisinone, **501**
 Nitrates, 103
 Nitric oxide, 93
Nitrocine, 103
 Nitrofurantoin, **303**, 304
 urinary infections
 prophylaxis, 259
 treatment, 252
Nitronal, 103
 Nitroprusside *see* Sodium nitroprusside, 91, **93**
 Nitrous oxide, **640**
 clinical procedures, 642
 Nitrous oxide-oxygen, 640
Nivaquine, 343
Nivestim, 462
Nizoral
 scalp, 590
 tablets—*discontinued*
 Nocturnal enuresis, 416
 Nonacog alfa, 123
 Non-convulsive status epilepticus, 236
 Non-depolarising muscle relaxants
 see Muscle relaxants
 Non-medical prescribing, 830
 Non-nucleoside reverse transcriptase inhibitors, 313, 314, 322
 Nonoxinol, 411
 Noonan syndrome, 389
 Noradrenaline, **111**
 infusion table (neonatal), 825
Norcuron, 651
NordiFlex, 390
Norditropin, 390
 Norelgestromin, ethinylestradiol with, 405
 Norepinephrine *see* Noradrenaline
 Norethisterone
 contraception, 409
 ethinylestradiol with, 406, 407
 mestranol with, 406
 parenteral, 410
 delayed puberty, **384**
 menstrual disorders, 384
 Norethisterone enantate, 409
Norgalax Micro-enema, 59
 Norgestimate, ethinylestradiol with, 406
Norgeston, 409
 Norgestrel *see* Levonorgestrel
Noriday, 409
Norimin, 406
Norimode (loperamide), 46
Norinyl-1, 406
Noristerat, 409, 410
Normacol preparations, 58
 Normal immunoglobulin *see* Immunoglobulins, normal, 628, **629**, 630
 Normal saline *see* Sodium chloride
Normasol, 600
Normax, 59
Normosang, 502
 Nortriptyline
 depression, **186**
 nocturnal enuresis, **186**
Norvir, 321
Norvil (metronidazole), 300
 Nose *see* Nasal
 Notifiable diseases, 246
Novaplex T 380 devices, 413
Novasource preparations, 772, 775
Nova-T, 413
Novgos—discontinued
NovoMix 30, 362
NovoPen products, 364
NovoRapid, 360
NovoSeven (factor VIIa fraction), 122
Noyada, 100
Nozinan, 175
 NPH *see* Insulin, isophane
 NSAIDs (non-steroidal anti-inflammatory drugs) *see* Analgesics
 NTBC *see* Nitisinone, **501**
 Nucleoside analogues *see* Nucleoside reverse transcriptase inhibitors, 313, 314, 315
 Nucleoside reverse transcriptase inhibitors, 313, 314, 315
Nuelin SA, 141
Nurofen (ibuprofen) preparations, 508
 Nurse independent prescribing, 830
 Nurse Prescribers' Extended Formulary, 830
 Formulary, 828
Nu-Seals Aspirin, 119
Nutilis preparations, 787, 789, 807
Nutramigen preparations, 792, 793
Nutraplus, 560
Nutricrem, 789
Nutrin preparations, 778, 780, 781, 782
Nutriplen preparations, 786, 789
Nutripren preparations, 778
Nutrison preparations, 772, 773, 775, 777
 soya formula, 773
 Nutrition
 ACBS, foods, 771
 enteral, 474, 475, 771
 intravenous, 472
 oral, 474, 475
 total parenteral, 472
Nutrizym 22, 71
NutropinAq, 390
NuvaRing, 405
Nystaform, 595
Nystaform-HC, 567
Nystan, 552
 Nystatin, 309
 mouth, 551, **552**
 palliative care, 18
 skin, 594, **595**
 chlorhexidine and hydrocortisone with, 567
 clobetasol and neomycin with, 569
 hydrocortisone with, 567

O

- Obesity, 191
 Obstetric surgery, antibacterial prophylaxis, 260
Occlusal, 586
Octagam, 630
Octanate (factor VIII fraction), 122
 OctaplasLG (fresh frozen plasma), 123
Octaplex (dried prothombin complex), 122
Octasa, 50
Octim, 392
 Octocog alfa, 123
 Octreotide, **368**, 369
 chronic hypoglycaemia, 368
 hyperinsulinaemic hypoglycaemia, 369
 varices, bleeding from, 369, 391
 Octylcyanoacrylate, 599
Ofufen, 540
Ocusan, 538
 Oedema
 cerebral, 80, 380
 pulmonary, 75
 Oesophageal varices, 391
 Oesophagitis *see* Gastro-oesophageal reflux disease, 34
 Oestrogens
 hormone therapy, 383
 labial adhesions, 398
 oral contraceptives, 401
 Ofloxacin
 ear, 544
 eye, 524, 526
Oftaquix, 526
Oilatum preparations, 559, 562
 Oily cream, 558
 Ointments
 definition, 557
 eye, 523
 suitable quantities, 557
 Olanzapine, **179**
 psychosis, 171
 Oligospermia, 388
 Olive oil, ear, 544, 545
 Olopatadine, 528, **529**
 Olsalazine, 47, 49, **51**
 Omalizumab, **157**
 Omeprazole, 43, **44**, 45
Omicur (amorolfine), 594
Omnitest products, 371
Omnitrope, 390
Oncaspar, 432
 Onchocerciasis, 354
Oncovin, 432
 Ondansetron, 193, **197**, 198
 palliative care, 19
Ondemet (ondansetron), 198
One Touch products, 371
One-Alpha, 488
Onkotrone, 427
 Onychomycosis *see* Fungal infections, skin, 305, 594
Opatanol, 529
Opiodur (fentanyl), 208

Opioid analgesics *see* Analgesics, opioid

Opioid antagonists

- poisoning in, 27
- postoperative, 653

OptiChamber devices, 143

Opticrom preparations, 530

OptiFlo preparations, 418

Optilast, 529

Optivate (factor VIII and von Willebrand factor concentrate), 122

Optive, 537

Optometrist independent prescribing, 830

OPV *see* Poliomyelitis, immunisation, 623

Oral balance see Biotène

Oralbalance, 554

Oral contraceptives *see* Contraception, oral

Oral glucose tolerance test, 372

Oral Impact, 787

Oral rehydration salts, 466

- WHO formula, 466

Oral rehydration therapy, 466

Oral syringes, 2

Oraldene, 553

Oramorph preparations, 209

Orap, 176

Orbifen (ibuprofen), 508

Orelox—discontinued

Orencia, 515

Orfadin, 501

Organophosphorus insecticides, poisoning by, 32

Orgaran, 116

Orgran products, 809, 810

Orlistat, **191**

Oroeeze (benzylamine), 550

Oropharynx

- infections, 551
- ulceration and inflammation, 549

ORS *see* Oral rehydration salts

ORT *see* Oral rehydration therapy, 466

Ortho All-Flex diaphragm, 413, 414

Orthopaedic surgery, antibacterial prophylaxis, 260

Oseltamivir, 330, **331**

Osmanil (fentanyl), 208

Osmolite preparations, 773, 776, 777

Osteoarthritis, 504

Osteomyelitis, 254, 287, 288

Osteonecrosis of the jaw, 394

Osteoporosis, 393, 394

- calcitriol, 487
- corticosteroid-induced, 393

Otex, 545

Otitis externa, 541

- antibacterial choice, 256

Otitis media, 544

- antibacterial choice, 256

Otomize, 542

Otosporin—discontinued

Otradrops (xylometazoline), 548

Otrivine (xylometazoline), 548

Otrivine-Antistin, 529

Ovranette, 406

Ovysmen, 406

Oxactin (fluoxetine), 187

Oxandrolone, 384, **387**

Oxazolidinone antibacterials, 290

Oxcarbazepine, 219, 220, **221**, 222

Oxis, 136

Oxyal, 538

Oxybuprocaine, **535**

Oxybutynin, **415**, 416

Oxycodone, **210**, 211

- palliative care, 16
- morphine equivalence, 17

OxyContin, 211

Oxygen, 162

- ambulatory therapy, 163
- arrangements for supply, 163
- asthma acute, 163
- cluster headache, 215
- nitrous oxide and, 640

Oxymetazoline, 548

Oxymetholone, 454

Oxymycin (oxytetracycline), 280

OxyNorm, 211

Oxytetracycline, **280**

- acne, 584
- oral infections, 278

P

Paediasure preparations

- enteral feeds, 780, 782, 783
- nutritional supplements, 784

Paediatric life support algorithms, *inside back cover*

Paediatric Seravit, 806

Pain

- bone, 200
- dental, 199, 205, 505
- dressing changes, 640
- ear, 542, 544
- musculoskeletal, 199
- neuropathic, 213
- orofacial, 199, 205, 213, 505
- palliative care, 16

 - breakthrough, 16
 - neuropathic, 16

- peri-operative, 645
- postoperative, 205
- rheumatic, 504
- sickle-cell disease, 199
- urethral, 417
- visceral, 203

Palivizumab, **332**

Palladone preparations, 208

Palliative care

- breakthrough pain, 16
- continuous subcutaneous infusions, 19
- neuropathic pain, 16
- pain management with opioids, 16
- prescribing in, 16

Paludrine, 345

Paludrine/Avlocor, 343

Pamidronate disodium, **395**

Panadol (paracetamol) preparations, 201

Pancrease HL, 71

Pancreatin, 69, **70**, 71

Pancreatitis, chronic, 69

Pancrex preparations, 70, 71

Pancuronium, 648, **649**, 650

Panoxyl preparations, 581

Panthenol, 485

Pantothenic acid, 485

Papaveretum, **211**

Paracetamol

- febrile convulsions, 239
- migraine, 213

 - buclicine and codeine with, 203

- pain, 199, **200**, 201

 - codeine with, 201, 202
 - dihydrocodeine with, 202, 203
 - postoperative, 645
 - tramadol with, 203

- palliative care, 16
- poisoning by, 26
- post-immunisation pyrexia, 605

Paracodol (co-codamol 8/500), 202

Paraffin

- eye ointment, 537, 538
- liquid and white soft, 558
- white soft, 558
- yellow soft, 558

Parainfluenza virus, 332

Paraldehyde

- neonatal seizures, 219
- palliative care, 18
- status epilepticus, 236, **238**

Paraproteinaemias, 454

Parasitocidal preparations, 597

Parasympathomimetics

- anaesthesia, 651
- eye conditions, 535
- myasthenia gravis, 518

Paradelprin (indometacin), 509

Parenteral nutrition, 472

- supplements, 474

Parkinsonism, drug-induced, 172

Paromomycin, 348

Paronychia, 257, 594

Paroxysmal nocturnal haemoglobinuria, 459

Partial seizures *see* Focal seizures, 219

Parvolex, 27

Pastes, definition, 557

Patient group direction, 3

Patient information leaflets, 2

Pavacol-D (pholcodine), 166

Peak flow meters, 142

Peanut oil *see* Arachis oil

Pedea, 129

Pediacef, 610

Pediculosis, 597

Peditrace, 474

Pegasy, 445

Peginterferon alfa, **445**

Pelvic inflammatory disease, 253

Pemphigus, 376

- Penbritin*, 266
 Penciclovir, 326, **597**
 Penicillamine, **493**
 cystinuria, 493
 rheumatic disease, 512
 Wilson's disease, 493
 Penicillin G *see* Benzylpenicillin sodium, 261, **262**
 Penicillin V *see*
 Phenoxymethylpenicillin
 Penicillin VK *see*
 Phenoxymethylpenicillin
 Penicillinases, 263
 Penicillins, 261
 antipseudomonal, 268
 broad spectrum, 264
 hypersensitivity, 261
 penicillinase-resistant, 263
 penicillinase-sensitive, 261
Pentacarinat, 352
 Pentamidine isetionate, **351**, 352
 leishmaniasis, 348, 351
 pneumocystis pneumonia, 350, 351
 trypanosomiasis, 351
Pentasa, 50
 Pentastarch, 471, 472
Pentostam, 349
Pepdite preparations, 793, 794, 795
 Peppermint oil, 39, **40**
Peptac, 37
Peptamen preparations, 773, 777, 781, 783
Peptisorb preparations, 773
 Perampanel, **226**
Perative, 777
Perfalgan, 201
Perfan, 74
 Periapical abscess, 255
 Pericazine *see* Pericyazine, **175**, 176
 Pericoronitis, 255
 Pericyazine, **175**, 176
Perinal, 66
 Periodontal abscess, 255
 Periodontitis, 550
 antibacterial treatment, 255
Periostat, 550, 551
 Peritonitis, 249
 Permethrin, 597, **598**, 599
Permitabs, 602
Peroxyl, 554
 Perphenazine
 nausea and vomiting, 192, **195**
 psychosis, **176**
Persantin preparations, 119
Personal Best, 142
 Pertussis
 immunisation, **621**
 pregnancy, 621
 prophylaxis, 258
 vaccines, combined, **610**, 611, 621
 Pethidine, 204, 205, **212**
 Petroleum jelly, 558
Pevaryl, 595
Peyona, 162
 PGD *see* Patient group direction, 3
 PGI₂ *see* Epoprostenol
 Phaeochromocytoma, 86, **98**
 Pharmacist independent prescribing, 830
Pharmalgen, 156
Pharmorubicin preparations, 427
 Pharyngitis *see* Throat infections
 Pharynx *see* Oropharynx
Pheburane, 500
Phenergan preparations, 156, 170
 Phenobarbital
 epilepsy, 219, **226**, 227
 status epilepticus, **238**, 239
 neonatal abstinence syndrome, 242
 neonatal seizures, 219
 palliative care, convulsions, 18
 poisoning, elimination, 24
 Phenobarbitone *see* Phenobarbital
 Phenothiazines
 nausea and vertigo, 193
 nausea and vomiting, 192, 193
 poisoning by, 30
 psychosis, 171
 Phenoxylbenzamine, **98**
 Phenoxymethylpenicillin, **262**, 263
 pneumococcal infection prophylaxis, 259
 rheumatic fever prophylaxis, 258
*Phenylalanine*50, 815
 Phenylephrine
 eye, **531**
 hypotension, **111**, 112
 local anaesthesia, lidocaine with, 658
 Phenylketonuria, 475, 815
 Phenytoin
 epilepsy, 219, 227, **228**
 status epilepticus, 236, **239**
 neonatal seizures, 219
Phlexy-10, 816
Phlexy-Vits preparations, 816
 Pholcodine, **166**, 167
Phosex, 482
 Phosgene, poisoning by, 32
 Phosphate-binding agents, 481
 Phosphates
 constipation, 61, 62, 63
 hypophosphataemia, **480**, **481**
 supplements, 480, 481
Phosphate-Sandoz, 481
 Phosphodiesterase inhibitors
 type-3, cardiovascular, 74
 type-5, pulmonary hypertension, 94, 95
 Phosphorus, 480
 Photochemotherapy, psoriasis, 574
 Photodamage, skin, 589
 Photodermatoses, 588
 ACBS, 819
 Phototherapy, psoriasis, 574
Phyllocontin Continus, 142
Physeptone (methadone), 208
 Physiological saline *see* Sodium chloride
Phytex, 596
 Phytomenadione, 117, 491, 492
Picolax, 64
 Picosulfate *see* Sodium picosulfate
Piko-1, 142
 Pilocarpine, **535**
 Pimecrolimus, 578, **579**, 580
 Pimozide
 psychosis, **176**
 Tourette syndrome, **176**, 241
Pinexel PR (tamsulosin), 415
Pinnactil (fluvastatin), 126
Pinnacle, 142
 Pinworm infections, 352
 Piperacillin
 tazobactam with, **268**
 Piperazine, arteminol with, **344**
 Piperazine—*discontinued*
Piracetam, 219, 236
Piriton, 155
 Piroxicam, 505, **510**
Pitressin—discontinued
 Pituitary
 function test, 388
 metyrapone, 396
 hormones, 387
 anterior, 387
 posterior, 390
 Pityriasis versicolor, 305, 594
 Pivmecillinam, **269**
 Pizotifen, **215**
PK Aid 4, 816
PK Foods products, 810, 811
PKU preparations, 815, 816, 817
 Plaque, 553
Plaquenil, 513
 Plasma
 concentrations, electrolytes, 463
 substitutes, 471
 Plasma, fresh frozen, 123
 Plasmapheresis, myasthenia gravis, 518
 Pneumococcal infection
 antibacterial prophylaxis, 259
 immunisation, vaccines, **622**, 623
 Pneumocystis pneumonia, 350
 prophylaxis, 350
 Pneumonia, 250, 251
 hospital-acquired, 251
 pneumococcal, 622
Pneumovax II, 622
Pocket Chamber, 143
Pocketpeak, 142
 Podophyllotoxin, **587**
 Poisoning
 active elimination, 24
 adsorbents, 24
 emergency treatment of, 23
 hospital admission, 23
 Poisons information services, *inside front cover*
 Poliomyelitis
 immunisation, 623
 travel, 623

Poliomyelitis (*continued*)—

- vaccines, **623**
- combined, 610, 611

Pollen extracts, 156

Pollinex, 157Polyacrylic acid *see* Carbomers, 536

Polyarteritis nodosa, 377

Polycal, 801

- glucose tolerance test, 372

Polyene antifungal drugs, 309

Polyethoxylated castor oil *see*

- Polyoxyl castor oil

Polyethylene glycols, 61, 63

Polyfax, 592

Polymethylmethacrylate, 599

Polymyositis, 513

Polymyxins

- ear, 544
- eye, 524, 528
- inhalation, **292**
- skin, 591, **592**
- systemic, 291, **292**

Polyoxyl castor oil, presence of, 3

Polyps, nasal, 545

Polysaccharide-iron complex, 450

Polystyrene sulfonate resins, 465

Polytar

- Emollient*, 576
- Liquid*, 591
- Plus*, 591

Polyvinyl alcohol, 538

Pompe disease, 497

Ponstan preparations, 509POP *see* Progestogens, contraceptives, oral, 401, 405, **408**

Poractant alfa, 162

Porphyrias, acute

- drugs to be avoided in, 502
- management of, 502

Postmenstrual age *see* Corrected

- gestational age, xiv

Potassium acid phosphate, 481

Potassium bicarbonate, 466, **467**

- tablets, effervescent, 467

Potassium canrenoate, 79, **80**

Potassium chloride

- infusion
 - glucose and, 470
 - sodium chloride and, 470
 - sodium chloride, glucose and, 470

- oral, **464**

- parenteral, **469**, 470

Potassium citrate, 417

Potassium iodide, 374

Potassium permanganate, 572, 599, **602**

Potassium supplements, 464

Povidone-iodine

- skin, 599, **601**
- shampoo, 590

Prader-Willi syndrome, 388, 389

Pralidoxime chloride, **32**

Pramocaine [ingredient], 65, 66

Praxoxine *see* PramocainePravastatin, 124, **126**

Praziquantel

- schistosoma, 353
- tapeworm, 353

Prazosin, **97**, 98

Precocious puberty, 385

Pred Forte, 528Prednisolone, 376, **382**, 383

- asthma, acute, 132
- Crohn's disease, 53
- ear, 543
- eye, 528
- haemorrhoids, 66
- hepatitis, 382
- infantile spasms, 219, 382
- inflammatory and allergic disorders, 382
- malignant disease, 437
- nephrotic syndrome, 382
- palliative care, 17, 18
- pneumocystis pneumonia, 350
- rectal, 53, 66
- ulcerative colitis, 53
- withdrawal of, 378

Predsol

- ear, 543
- eye, 528
- rectal, 53

Pre-eclampsia, 91

Pregabalin

- epilepsy, 219

Pregestimil, 794

Pregnancy

- anticoagulants, 117
- antihistamines, 152
- asthma, 131
- corticosteroids, 379
- cytotoxic drugs, 421
- epilepsy and, 218
- folate supplements, 452
- HIV infection, 313
- hypertension in, 91
- immunosuppressants, 436
- iron, 448
- malaria, 335
 - prophylaxis, 336
 - treatment, 335
- nausea and vomiting, 193
- prescribing in, 15
- tuberculosis and, 295
- urinary infections, 303

Pregnyl, 388

Premedication, 640, 642

Prescribing

- ACBS, 771
- breast-feeding, 15
- children, 1
- controlled drugs, 9
- hepatic impairment, 13
- independent, 830
- instalments, 9
- palliative care, 16
- pregnancy, 15
- renal impairment, 13
- repeat prescriptions, 9
- supplementary, 830

Prescription forms

- controlled drugs, 8

Prescription forms (*continued*)—

- European Economic Area (EEA), 3
- nurses, 828
- security, 3
- Switzerland, 3

Prescription only medicines *see* preparations identified by ^(PoM)

- throughout *BNF for Children*

Prescription writing, 4

Presinex (desmopressin), 392

Pre-thickened infant feeds, 797

Prevenar 13, 622, 623*Prezista*, 320*Priadel*, 183

Prices, xvi

Prilocaine, **658**, 659

- dental, 659
- felypressin with, 655, 659
- lidocaine with, 657, 658

Primacine (erythromycin), 286*Primacor*, 75

Primaquine

- malaria treatment, 335, **345**
- pneumocystis pneumonia, 350

Primaxin, 276*Primene*, 473Primidone, 226, **227***Primolut N*, 384*Priorix*, 619*Pripsen*—discontinued*Privigen*, 630*Pro-Banthine*, 39

Procaine benzylpenicillin, 253, 261

Pro-cal preparations, 805Procabazine, **434***Proceli* products, 808, 809, 810Prochlorperazine, 192, 193, **195**, 196*Proctofoam HC*, 66*Proctosedyl*, 66Procyclidine, **241***Prodose*, 95

Product licence, 2

Pro-Epanutin, 237

Proflavine cream, 599

Progesterone

- hormone therapy, 384

Progestogen-only pill *see*

- Progestogens, contraceptives, oral, 401, 405, **408**

Progestogens

- contraceptives
 - emergency, 413, 414
 - intra-uterine, 410, **411**
 - oral, 401, 405, **408**
 - parenteral, **409**
 - hormone therapy, 384

Prograf, 442Proguanil, **345**

- atovaquone with, 345, 346
- chloroquine with, 343
- malaria prophylaxis, 336, 345

Promethazine

- allergic disorders, 152, **156**
- hypnotic, **169**, 170
- motion sickness, 193

Promethazine (*continued*)—
 nausea and vomiting, 193,
194
 sedation, **169**
 Promethazine teoclate, **194**, 195
 Promin products, 810, 811
 Promixin, 292
 Propamidine isetionate, eye, 524,
526
 Propantheline, 38, **39**
 Prophylaxis, antibacterial, 258
Propionibacterium acnes, 582
 Propionic acidaemia, 814
 Propofol, 635, **637**, 638
Propofol-Lipuro, 638
Propoven (propofol), 638
 Propranolol, **87**
 cardiovascular, 87
 hyperthyroidism, 375
 migraine prophylaxis, **87**, 215
 see also Beta-adrenoceptor
 blocking drugs
 tetralogy of Fallot, 87
 thyrotoxicosis, 374, 375
 tremor, 241
 Propylene glycol, presence of, 3
 Propylthiouracil, 373, **374**, 375
ProSource preparations, 803, 804
 Prostacyclin *see* Epoprostenol
 Prostaglandins
 anticoagulant, 116
 ductus arteriosus, 130
 eye, 531, 532
Prostap preparations, 387
Prostin E2, 130
Prostin VR, 130
ProSure, 800
Prosurin XL (tamsulosin), 415
 Protamine sulfate, 113, **118**
 Protease inhibitors, 313, 314, 319
 Protein
 intravenous nutrition, 473
 urinalysis, 369, 372
 Protein C concentrate, 123
 Prothionamide *see* Protionamide,
 296
 Prothrombin complex, dried, **122**
Protifar, 803
 Protionamide, 296
 Proton pump inhibitors, 43
Protopam, 32
Protopic, 580
 Protozoal infections, 334
Proveblue, 24
ProvideXtra, 784
 Proxymetacaine, **535**, 536
 fluorescein with, 536
Prozac, 187
Prozep (fluoxetine), 187
ProZero, 815
 Pruritus
 ACBS, 818
 cholestasis, 69
 palliative care, 19
 perianal, 65
 skin, 152, 563
 Pseudoephedrine, **167**

Pseudomembranous colitis
 antibacterial therapy
 metronidazole in, 299
 vancomycin in, 289
Pseudomonas aeruginosa infections,
 268, 270, 277, 280, 291
 eye, 524
 Psittacosis, 277
 Psoralen, 574
 Psoriasis, 573
 corticosteroids, 565
 photochemotherapy, 574
Psoriderm preparations, 576
 scalp, 590
Psorin preparations, 577
 Psychiatric reactions
 corticosteroids, 378
 Psychoses, 170
 Puberty
 delayed, 383, 384, 388
 precocious, 385, 387
 Pubic lice, 598
Pulmicort preparations, 147
 Pulmonary
 hypertension, 93, 116
 oedema, 75, 77, 79
 surfactants, 162
Pulmozyme, 165
Pulvinol
 beclometasone, 146
 salbutamol, 138
Pure products, 809
Puri-Nethol, 429
 Purpura, thrombocytopenic, 460
 PUVA, 574
 Pyelonephritis, 303
Pyravex, 551
 Pyrazinamide, **297**
 tuberculosis treatment, 294,
 295, 296
 Pyrexia
 post immunisation, 605
 Pyridostigmine, 518, **519**
 Pyridoxine
 anaemias, 454
 isoniazid-induced neuropathy,
 486
 metabolic disorders, 485, **486**
 seizures, 219, 485, 486
 status epilepticus, 236
 Pyrimethamine
 malaria, 346
 sulfadoxine with, 334, 346
 toxoplasmosis, **349**
 Pyrethione zinc shampoos, 590
 Pyruvate dehydrogenase defects,
 500

Q

Q-fever, 277
Qlaira, 407
QuantIFERON-TB Gold, 609
 Quaternary ammonium
 compounds, 38
Questran preparations, 127
 Quetiapine, 171, **179**, 180

Quinine, **346**, 347
 malaria, 334, 335, 346
 poisoning, elimination, 24
Quinoderm, 581
 Quinolones, 301
 ear, 544
 eye, 524
Quinoric (hydroxychloroquine),
 513
 QV preparations, 559, 562
Qvar preparations, 146
R
 Rabies
 immunisation, 623
 immunoglobulin, 631
 travel, 632
 vaccine, **624**
Rabipur, 624
Racecadotril, **47**
Raltegravir, 314, **325**
Ranitit (ranitidine), 42
Ranitidine, **42**
Rapamune, 440
Rapifen, 646
Rapilose preparations
 hypoglycaemia, 367
 oral glucose tolerance test,
 372
Rapitil, 529
Raporsin XL (doxazosin), 97
Rasburicase, **422**
Ratiograstim, 462
 Raynaud's syndrome, 104, 108
Rebetol, 333
 Red eye, 525, 527
Redoxon, 487
ReFacto AF (factor VIII fraction),
 123
Reflexions diaphragm, 413
 Reflux oesophagitis *see* Gastro-
 oesophageal reflux disease, 34
Refolinon (calcium folinate), 423
Regulan, 57
 Rehydration
 oral, 466
 parenteral, 468
Relaxit, 63
Relenza, 332
Relestat, 529
Relvar Ellipta, 149
Remedeine preparations, 202, 203
Remicade, 56
 Remifentanyl, 204, 645, **646**, 647
Renagel, 482
 Renal
 excretion, interactions
 affecting, 660
 impairment, prescribing in, 13
Renamil, 800
Renapro, 800
Renastart, 800
Renilon, 789
Repevax
 immunisation
 childhood, 610
 pregnancy, 611
Replagal, 495

Replenine-VF (factor IX fraction), 123

Resonium A, 465

Resource preparations

enteral feed, 776, 782

feed thickener, 807

fibre supplement, 806

nutritional supplement, 784, 787, 789, 790

Respiratory

depression

poisoning, 23

postoperative, 653

distress syndrome, 75, 77

pulmonary surfactants, 162

failure, 161

secretions, excessive (palliative care), 18

stimulants, 161

syncytial virus infections, 332

Respontin, 140

Restandol, 385

Restlessness, palliative care, 19

Resuscitation

cardiopulmonary, 112

dental practice, 635

Retacrit, 456

Retapamulin, 591, **592**

Retinoids

acne

oral, 584

topical, 582

leukaemia, 435

psoriasis, 574, **577**

Retinol *see* Vitamin A

Retrovir, 319

Revatio, 96

Revaxis, 611

Rexocaine, 657

Reyataz, 320

Rheumatac Retard (diclofenac), 507

Rheumatic diseases, 504

corticosteroid injections, 511

Rheumatic fever, prophylaxis, 258

Rhinitis, allergic, 545

Rhinocort Aqua, 546

Rhinolast preparations, 545

Rhumalgan CR (diclofenac), 507

Riamet, 334, 342

Riastap (fibrinogen, dried), 123

Ribavirin, **333**

chronic hepatitis C, 330, 332

Lassa fever, 332

respiratory syncytial virus, 332

Riboflavin, 485

Rickets, 487

hypophosphataemic, 480, 487

Rickettsia, 277

Rifabutin, 296, **298**

Rifadin, 299

Rifampicin, **298**, 299

Haemophilus influenzae

prophylaxis, 258

isoniazid and pyrazinamide with, 299

isoniazid with, 299

Rifampicin (*continued*)—
meningococcal meningitis
prophylaxis, 258
tuberculosis, 294, 296

prophylaxis, 259
treatment, 295

Rifamycins, 294, 296, 298

Rifater, 299

Rifinah preparations, 299

Rigevidon, 406

Rimacillin (ampicillin), 266

Rimactane, 299

Rimafen (ibuprofen), 508

Rimepam (diazepam), 521

Rimapurinol (allopurinol), 422

Rimoxallin (amoxicillin), 265

Rinatec, 549

Ringer-Lactate solution, 469

Ringer's solution, 469

Ringworm infection *see*

Dermatophyte infection, 305, 594

Risedronate sodium, **395**, 396

Risperdal preparations, 180

Risperidone

aggression, **180**

mania, **180**

psychosis, 171, **180**

Ritalin, 190

Ritonavir, 314, **321**

lopinavir with, 321

see also Kaletra, 321

Rituximab, 444

Rivotril, 236

injection—*discontinued*

Rizopia products, 810

Roaccutane, 586

RoActemra, 517

Robinul powder, 602

Rocaltrol, 489

Rocephin, 274

Rocuronium, 648, **650**

Roferon-A, 445

Ropivacaine, **659**

Rosacea, 581

Rosiced, 593

Rosuvastatin, 124, **126**

Rotarix, 624

Rotavirus vaccine, **624**

Roundworm infections, 353

Rozex, 594

rt-PA *see* Alteplase, **120**

Rubella

immunisation, 625

immunoglobulin, 629

vaccines, combined, 618, 619

Rufinamide, 219, **229**

Rupafin, 154

Rupatadine, 152, **154**

Rusyd (furosemide), 78

Rynacrom preparations, 547

Salamol (salbutamol) preparations, 138

Salapin (salbutamol), 137

Salatac, 586

Salazopyrin, 52

Salbulin Novolizer, 138

Salbutamol, 135, **137**

asthma, acute, 132

hyperkalaemia, 137

Salcatonin *see* Calcitonin, 393, **394**, 479

Salicylates, aphthous ulcers, 551

Salicylic acid, **577**

betamethasone with, 568

fungal infections, 596

hyperkeratoses, 586

psoriasis, 573

coal tar and dithranol

with, 577

coal tar with, 590

dithranol with, 577

zinc with, 577

scalp, 590

warts and calluses, 586

Saline *see* Sodium chloride

Saliva, artificial, 554

Saliveze, 554

Salivix, 555

Salmeterol, **138**, 139

fluticasone with, 149

Salmonellosis, 248

Salofalk preparations, 51

Salpingitis, 277

Salt substitutes, 464

Sandimmun, 440

Sandocal, 478

Sando-K, 464

Sandostatin, 369

Sanomigran, 215

elixir—*discontinued*

Santizor XL (tolterodine tartrate), 416

Sapropterin, **475**

Savlon Dry powder, 601

SAYANA PRESS, 409, 410

Scabies, 597

Scandishake, 805

Scandonest preparations, 658

Scheriproct, 66

Schistosoma, 353

Schistosomicides, 353

Schizophrenia, 171

School, managing medicines at, 2

Scopoderm preparations, 199

Scopolamine *see* Hyoscine

Scottish Medicines Consortium, 3

Scurvy, 486

SD CodeFree products, 371

Seasonal influenza vaccines, 617

Sebc, 576

Sebomin MR, 279

Seborrhoeic

dermatitis, 572

eczema, 572

Securon preparations, 108

Sedation, clinical procedures, 642

Sedatives, 168

see also Anxiolytics, 168, 170

- Segawa syndrome, 239
- Seizures
- absence, 219
 - neonatal, 219
 - see also* Epilepsy
- Selenium sulfide, 590, 594
- Selexid*, 269
- Selsun*, 590
- Semisodium valproate, 181
- Senna, **60**
- Senokot*, 60
- Sensocard* products, 371
- Septanest*, 656
- Septic
- arthritis, 255
 - spots *see* Paronychia, 257, 594
- Septic shock, 376
- Septicaemia, 254
- catheter-related, 254
 - hospital-acquired, 254
 - meningococcal, 254
- Septtrin*, 293
- Serenace*, 175
- Seretide*, 149
- Serevent*, 139
- diskhaler*—discontinued
- Seroquel* preparations, 180
- Serotonin re-uptake inhibitor antidepressants *see* Antidepressants, serotonin re-uptake inhibitors, 183, 186
- Sertraline, 186, **188**
- Sesame oil, presence of, 3
- Setofilm* (ondansetron), 198
- Sevelamer hydrochloride, 481, **482**
- Sevoflurane, **639**
- Sevredol*, 209
- Sex hormones
- androgens, 384
 - oestrogens, 383
 - progestogens, 384
- Sexual dysfunction, antipsychotics and, 172, 173
- Shampoos, 590
- Shared care, 4
- Shigellosis, 248
- Shingles, 326
- Shock, 109
- anaphylactic, 158
 - blood-volume expansion, 471
 - cardiogenic, 109
 - hypovolaemic, 109
 - metabolic acidosis, 470
 - septic, 109, 376
 - neonatal, 109
- Short stature homeobox-containing gene deficiency, 388
- Shower preparations
- antimicrobial with, 562
 - emollient, 561, 562
- SHOX deficiency *see* short stature homeobox-containing gene deficiency, 388
- Sickle-cell disease, 456
- delayed puberty, 383
 - pain, 199
 - pneumococcal infection prophylaxis, 259
- Significant changes, xvii
- Siklos*, 457
- Sildenafil, 94, **95**, 96
- Silk clothing, 572
- Silkis*, 575
- Silver nitrate, 586, **587**
- Silver sulfadiazine, **592**, 593
- Simeticone, **36**
- aluminium hydroxide with, 36
 - hydrocalcite with, 36
 - magnesium hydroxide with, 36
- Similac* preparations, 780, 794
- Simple eye ointment, 538
- Simple linctus, 167
- paediatric, 167
- SimpleXx*, 390
- Simulect*, 439
- Simvador* (simvastatin), 126
- Simvastatin, 124, **126**
- ezetimibe with, 127
- Sinemet* preparations, 240
- Sinepin*, 185
- Singulair*, 151
- Sinusitis, 548
- antibacterial treatment, 256
- Siopel*, 563
- Sirolimus, 438, **440**
- Skin preparations
- ACBS, 818
 - antibacterials, 591
 - antiviral, 596
 - barrier, 563
 - camouflagers, 589
 - cleansing, 599
 - corticosteroids, 564
 - dilution, 557
 - emollient, 558
 - excipients, 557
 - ulcers, 602
- Skinoren*, 582
- SLO Drinks*, 807
- Slocinx XL* (doxazosin), 97
- Slofenac SR* (diclofenac) preparations, 507
- Slo-Phyllin*, 141
- Slo-Pro* (propranolol), 88
- Slow-K*, 464
- Slow-Sodium*, 466
- SMA* preparations, 778, 779
- low lactose, 794
 - thickened, 797
- Smallpox vaccine, 625
- SMC *see* Scottish Medicines Consortium, 3
- Smith-Lemli-Opitz syndrome, 68
- Smoking cessation, 242
- Snake bites, 33
- antivenom, 33
- Sno Tears*, 538
- Sno-Pro*, 815
- Soap substitutes, 558
- Sodiofolin*, 423
- Sodium acid phosphate, 481
- Sodium alendronate *see* Alendronic acid, **394**, 395
- Sodium amidotrizoate, 65
- Sodium benzoate, 498, **499**
- Sodium bicarbonate
- cyanosis, 87
 - ear wax removal, 544, 545
 - intravenous, 470
 - oral, 466, 467
- Sodium calcium edetate, 31
- Sodium calcium edetate *see* Sodium calcium edetate, 31
- Sodium chloride
- bladder instillation, **418**
 - bladder irrigation, 417, 418, 600
 - electrolyte replacement
 - oral, 465, 466
 - parenteral, 468
 - eye irrigation, 524, **538**, 539
 - hypercalcaemia, 479
 - hypertonic inhalation, 164
 - infusion, 468
 - glucose and, 468
 - potassium chloride and, 470
 - potassium chloride, glucose and, 470
 - mouthwash, 553, 554
 - compound, **554**
- nasal
- congestion, 548
 - postoperative douche, 545
- nebuliser solution
- hypertonic, 165
 - isotonic, 144
- skin cleansing, 599, **600**
- Sodium citrate
- bladder irrigation, 417
 - rectal, 63
- Sodium clodronate, 396
- Sodium content, antacids, 35
- Sodium cromoglicate
- asthma, **150**
 - eye, 528, **530**
 - food allergy, **56**
 - nose, 545, **547**
- Sodium cromoglycate *see* Sodium cromoglicate
- Sodium dichloroacetate, **501**, 502
- Sodium docusate *see* Docusate sodium
- Sodium feredetate, 449, 450
- Sodium fluoride, **482**, 483
- Sodium fusidate, **288**
- angular cheilitis, 552
 - mouth, 552
- Sodium hyaluronate, **538**, 539
- tear deficiency, 538
- Sodium iodine, radioactive, 374
- Sodium ironedetate *see* Sodium feredetate, 449, 450
- Sodium lactate
- intravenous infusion
 - compound, 468, 469
- Sodium nitrite, 31
- Sodium nitroprusside, 91, **93**
- Sodium oxybate, 30
- Sodium phenylbutyrate, 498, 499, 500
- Sodium picosulfate, **60**
- magnesium citrate with, **64**

- Sodium picosulphate *see* Sodium picosulfate
- Sodium pidolate, 559
- Sodium polystyrene sulfonate, 465
- Sodium stibogluconate, **348**, 349
- Sodium thiosulfate, 31
- Sodium valproate *see* Valproate
- Sofradex*
- ear, 543
 - eye, 528
- Soft tissue disorders, 504
- Solaraze*, 589
- Solian*, 177
- Solivito N*, 474
- Solpadol* (co-codamol 30/500), 202
- Solu-Cortef*, 382
- Solu-Medrone*, 382
- Solvazinc*, 483
- Solvents, ear wax removal, 544
- Somatomedins, 397
- Somatotrophin, 389
- Somatotropin, **389**, 390
- Sorbisteri*, 465
- Sorbitol, presence of, 3
- S.O.S. preparations*, 801
- Sotacor*, 90
- Sotalol, 81, 86, **90**
- arrhythmias, 81, 86
 - see also* Beta-adrenoceptor blocking drugs
- Soya oil, 561
- Soya-based infant formula, 796
- Soybean oil, tear deficiency, **538**
- Space Chamber Plus*, 143
- Spacer devices, 143
- Spasm
- muscle, 520
 - vascular, 104, **107**
- Spasmonal preparations*, 39
- Spasticity, 520
- Specialist-importing companies, 840
- Special-order
- dermatological preparations, 556
 - manufacturers, 840
- Spermicides, 411
- SPF *see* Sun protection factor, 588
- Spiramycin, 284, 349, 350
- Spirit
- industrial methylated, 600
 - surgical, 600
- Spirolactone, **79**
- heart failure, 75
 - precocious puberty, 385
- Splenectomy *see* Asplenia
- Sporanox*, 308
- Sporanox-Pulse*, 308
- Sport, drugs and, 22
- Sprilon*, 563
- SSRIs *see* Antidepressants, serotonin re-uptake inhibitors, 183, 186
- SST*, 555
- Stamril*, 627
- Staphylococcal scalded skin syndrome, 257
- Starch, etherified, 471, 472
- Statins, 124
- Status epilepticus, 236
- Stavudine, 314, **317**
- Steam inhalations, 548
- Stefluvin XL* (fluvastatin), 126
- Stelazine*, 177
- syrup—*discontinued*
- Stemetil*, 196
- Sterculia
- constipation, 58
 - frangula with, 58
 - diarrhoea, 45
- Stericlens* (sodium chloride), 600
- Steri-Neb*
- ipratropium, 140
 - Salamol* (salbutamol), 138
 - sodium chloride, 144
- Steripod* (sodium chloride), 600
- Steripoule* (sodium chloride), 144
- Steroid treatment card, 379
- suppliers, 378
- Steroids *see* Anabolic steroids; Corticosteroids; Glucocorticoids; or Mineralocorticosteroids
- Stesolid* (diazepam), 237
- Stiemycin*, 582
- Still's disease *see* Arthritis, juvenile idiopathic, 512
- Stimulants
- central nervous system, 188
 - respiratory, 161
- Stings, 33
- Stiripentol, 219, **229**
- Stoma, drugs and, 67
- Stomatitis
- angular, 552
 - herpetic, 551
- Strattera*, 189
- Strefen*, 551
- Streptase*, 121
- Streptococcal infection, antibacterial prophylaxis, 258
- Streptokinase, **121**
- Streptomycin
- brucellosis, 299
 - endocarditis, 280
 - tuberculosis, 294, 296, **299**
- Stronazon MR* (tamsulosin), 415
- Strongyloidiasis, 354
- Stugeron*, 194
- Subcuvia*, 629
- Subgam*, 629
- Sublimaze*, 646
- Succimer, 31
- Succinylcholine *see* Suxamethonium, **651**
- Sucralfate, **42**, 43
- Sucrose, presence of, 2
- Sudafed*, 167
- Sudocrem*, 563
- Sugammadex, **652**
- Sugar-free, definition, 3
- Sugar-free liquid medicines *see* preparations identified by 'sugar-free' throughout *BNF for Children*
- Sulazine EC* (sulfasalazine), 52
- Sulfadiazine
- silver, 592
 - toxoplasmosis, 349, 350
- Sulfadoxine
- malaria, 346
 - pyrimethamine with, 334, 346
- Sulfamethoxazole, trimethoprim with, *see* Co-trimoxazole
- Sulfasalazine
- inflammatory bowel disease, 47, 49, **51**, 52
 - rheumatic disease, 512, **517**
- Sulfites, presence of, 3
- Sulfonamides, 292
- Sulfonylureas, 364
- Sulfur, 573
- Sulfur dioxide, poisoning, 32
- Sulpha... *see* Sulfa...
- Sulphasalazine *see* Sulfasalazine
- Sulphonamides *see* Sulfonamides, 292
- Sulphonylureas *see* Sulfonylureas, 364
- Sulpiride
- psychosis, **176**, 177
 - Tourette syndrome, **176**, 241
- Sulpur*, 177
- Sumatriptan
- cluster headache, **213**, 215
 - migraine, **213**, 214
- Sun protection factor, 588
- Sunscreens, 588
- ACBS, 819
- Sunsense Ultra*, 588
- Sunya 20/75*, 406
- Supercheck2* products, 371
- Superinfection, 248
- Suplena*, 800
- Supplementary prescribing, 830
- Suprax*, 272
- Suramin, 354
- Surfactants, pulmonary, 162
- Surgery
- antibacterial prophylaxis, 259, 260, 261
 - diabetes and, 358
 - long-term medication and, 634
 - tetanus vaccine, 625
 - wound infection, 257
- Surgical spirit, 600
- Survanta*, 162
- Survived preparations*, 773
- Sustanon*, 385
- Sustiva*, 322
- Suxamethonium, **651**
- Symbicort*, 144, 147
- Symbols and abbreviations, *inside back cover*
- Sympathomimetics
- asthma, 135
 - eye, 531, 533
 - inotropic, 108
 - vasoconstrictor, 110
- Synacthen*, 388
- Synacthen Depot*, 388
- Synagis*, 332
- Synalar preparations*, 570, 571
- Syner-KINASE*, 121
- Synflorix*, 622, 623
- Synphase*, 407

Syntaris—discontinued
Synthamin preparations, 473
 Syphilis, 253
Syprol (propranolol), 88
 Syringe drivers, palliative care, 19
 mixing and compatibility, 19
 problems, 20
 Syringes, oral, 2
Systane preparations, 537
Sytron, 450

T
Tabphyn MR (tamsulosin), 415
 Tacalcitol, 573, 574, **575**
 Tachycardias *see* Arrhythmias
Tacni, 443
 Tacrolimus
 eczema, 578, **580**
 immunosuppression, 438, **440**,
 442
 Taenicides, 353
Tambacor preparations, 85
Tamiflu, 331
 Tamsulosin, **415**
Tapclob (clobazam), 235
 Tapeworm infections, 353
 Tar, **575**
 see also Coal tar
Taranis products, 810, 811
 Tardive dyskinesia, 172
Targocid, 290
 Tartrazine, presence of, 3
 Tazarotene, 573
 Tazobactam
 piperacillin with, **268**
Tazocin, 268
 3TC *see* Lamivudine
 Tear deficiency, 536
 Tear gas, 32
Tear-Lac, 537
 Tears, artificial, 536
Tears Naturale, 537
Tegretol preparations, 221
 Teicoplanin, 288, **290**
 Telangiectasia, hereditary
 haemorrhagic, 383
Telfast, 153
Telzir, 320
 Temazepam
 palliative care, 17
 premedication, 642, 643, **644**
Temgesic, 205
Temodac (temozolomide), 433
Temodal, 433
 Temozolomide, **432**
 Tendinitis, 511
 Tennis elbow, 511
 Tenofovir
 chronic hepatitis B, **317**, 329
 HIV infection, 314, **317**
 efavirenz and
 emtricitabine with, 318
 emtricitabine with, 318
Tenormin, 88
Tenprolidel XL (quetiapine), 180
 TENS *see* Transcutaneous
 electrical nerve stimulation, 16

Tensipine MR, 106
Tensium (diazepam), 521
Tenrini preparations, 780, 783
Teoptic, 532
Tepadina, 426
 Teratology information service,
 inside front cover
 Terbinafine
 dermatophyte infections, 305,
 311
 systemic treatment, **312**,
 313
 topical treatment, 594,
 596
 Terbutaline, **139**
 asthma, 135
 acute, 132
 Terlipressin, 391, **393**
 Terminal care *see* Palliative care
Terra-Cortril, 567
 Testolactone, 385, **386**
 Testosterone, **385**
 enantate, 384, 385
 esters, 385
 propionate, 384, 385
 undecanoate, 384, 385
 Testotoxicosis *see* Puberty,
 precocious, 385, 387
 Tetanus
 antibacterial treatment, 261,
 299
 immunisation, **625**, 631
 immunoglobulin, **631**
 travel, 632
 vaccines, combined, 610, 611,
 625
 wounds, 625
 Tetracaine
 eye, 535, **536**
 local anaesthetic, **659**
 rectal, 65
 Tetracosactide, 219, 387, **388**
 Tetracosactrin *see* Tetracosactide,
 219, 387, **388**
 Tetracycline, 277, **278**
 acne, 584
 oral infections, 278
 skin, clobetasone butyrate
 with, 569
 Tetrahydrobiopterin, **475**
 Tetrahydrofolate reductase
 deficiency, 500
 Tetralogy of Fallot, 87
Tetralysal-300, 279
Tetraspan—discontinued
Tevagastim—discontinued
T-Gel, 591
 Thalassemia, 457
 THAM *see* Trometamol, **470**
 Theophylline, **140**, 141
 poisoning by, 30
 poisoning, elimination, 24
 see also Aminophylline
 Thiabendazole *see* Tiabendazole,
 354
 Thiamine, **485**, 486
 Thiazides, 75
 diabetes insipidus, 391
 see also Diuretics, 75

Thick and Easy, 807
Thicken Aid, 807
 Thickened foods, 807
 Thickened supplements, 786, 789
 Thioguanine *see* Tioguanine, 428,
 430
 Thiopental
 anaesthesia, 636, **638**
 status epilepticus, 236, **638**
 Thiopentone *see* Thiopental
 Thiopurine methyltransferase, 436
 Thiotepa, **426**
Thixo-D, 807
 Threadworm infections, 352
 Throat infections
 antibacterial treatment, 256
 fungal, 551
 gonorrhoea, 253
 viral, 551
 Thrombocytopenias, 454
 Thrombocytopenic purpura, 460
 immunoglobulins, 628
 prednisolone, 382
 Thrombo-embolism, 116
 Thrombolytics, 120
 Thrombosis, 113
 antiplatelet drugs, 118
 deep-vein, 113, 116
 prophylaxis, 113
 Thrush *see* Candidiasis
Thymoglobuline, 438
 Thyroid
 antagonists, 373
 hormones, 372
 storm, 374
 Thyroidectomy, 373
 Thyroiditis, Hashimoto's, 372
 Thyrotoxic crisis, 374
 Thyrotoxicosis, 373
 beta-blockers, 87, 374
 Thyrotoxicosis, neonatal, 374
 Thyroxine *see* Levothyroxine, **372**,
 373
 Tiabendazole, 354
 Tiagabine, 219, **229**, 230
 Ticarcillin, 268
 clavulanic acid with, 268, **269**
 Tick-borne encephalitis
 immunisation, 625
 travel, 632
 vaccine, **626**
TicoVac, 626
 Tics, 241
Tilade, 150
Tildiem preparations, 105
Tilofyl (fentanyl), 208
Tiloryth (erythromycin), 286
Timentin, 269
Timodine, 567
 Timolol, eye, **532**
 dorzolamide with, 534
Timoptol preparations, 532
 Tinea infections, 305, 594
 Tinidazole, 348
 amoebiasis, 347, 348
 giardiasis, 348
 protozoal infections, 348
 trichomoniasis, 348

Tinzaparin, 114, **115**
 Tioconazole, 594, **596**
 Tioguanine, 428, **430**
Tiopex, 532
 Tipranavir, 314, **322**
Tisept, 601
 Tissue adhesive, 599
 Tissue-type plasminogen activator
see Alteplase, **120**
 Titanium dioxide, 563, 588
Tivicay, 324
Tobi preparations, 283
Tobia products, 809
 Tobramycin, 280, **283**
 eye, 524, **527**
Tobravisc, 527
 Tocilizumab, 515, **517**
 Tocopherols, 490
 Tocopheryl, 490
 Toilet preparations, ACBS, 818
 Tolazoline, 93, 94, **96**
 Tolbutamide, 364, **365**
 Tolterodine, 415, **416**
 Tonic seizures, 219
 Tonic-clonic seizures, 219
 Tonsillitis *see* Throat infections
Topal—discontinued
Topamax, 231
 Topiramate
 epilepsy, 219, **230**, 231
 migraine, 215, **230**
Toradol, 645
 Torsade de pointes, 81
 magnesium sulfate, 479
 Total parenteral nutrition, 472
 Tourette syndrome, 241
 TOXBASE, 23
 Toxoplasma chorioretinitis, 349
 Toxoplasmosis, 349
 TPN *see* Total parenteral nutrition,
 472
 Trachoma, 277, 524
Tracleer, 94
Tracrium, 649
Tradorec XL (Tramadol), 213
Tramacet, 203
 Tramadol, 204, 205, **212**, 213
 palliative care, 16
 morphine equivalence, 17
 paracetamol with, 203
Tramquel SR (tramadol), 212
Trandate, 89
 Tranexamic acid, **121**, **122**
 palliative care
 capillary bleeding, 17
 mucosal bleeding, 18
 Tranquillisers, 168
 Transcutaneous electrical nerve
 stimulation, 16
 Transfusion reactions, 454
 Transplant rejection, 435, 436,
 438
Travasept-100, 601
 Travel, vaccination for, 632
 Travellers' diarrhoea, 632
 Travoprost, 532
 Treatment cards, anticoagulant,
 117

Tree pollen extracts, 156, 157
 Tremors, 241
 Tretinoin
 acne, 582, **583**
 erythromycin with, 583
 leukaemia, 435
Triadene, 407
 Triamcinolone
 intra-articular, 511
 rheumatic disease, 511,
 512
 nose, **547**
 skin, 571, 572
 Triazole antifungal drugs, 305
 Tribavirin *see* Ribavirin
 Trichomonads, 348
 Trichomonal infections, 348
 Tricyclic antidepressants *see*
 Antidepressants, tricyclic
 Trientine, 493, **494**
 Trifluoperazine
 anxiety, **177**
 nausea and vomiting, 192,
 196
 psychosis, **177**
 Trihexyphenidyl, **241**
 Tri-iodothyronine *see*
 Liothyronine, 372, **373**
 Triiodothyronine—*discontinued*
Trileptal, 222
 Trimethoprim *see* Alimemazine
 Trimethoprim, 293, **294**
 pneumocystis pneumonia, 350
 sulfamethoxazole with, *see* Co-
 trimoxazole
 urinary infections
 prophylaxis, 259
 treatment, 252
Trimopan (trimethoprim), 294
Trimovate, 569
TriNovum, 407
 Triptans *see* 5HT₁-receptor
 agonists, 213
 Triptorelin, **387**
TriRegol, 407
 Tris-hydroxymethyl
 aminomethane *see* Trometamol,
470
Tritamyl products, 809
Trizivir, 316
 Trometamol, **470**
 Tropical diseases, advice, 334
 Tropicamide, 530, **531**
Trosyl, 596
TRUEone, 371
TRUEresult products, 371
TRUEtrack products, 371
TRUEyou products, 371
Trusopt, 534
Truvada, 318
 Trypanocides, 349
 Trypanosomiasis, 349
T-Safe 380A devices, 413
T-SPOT.TB, 609
TT 380 Slimline, 413
 Tub/BCG, Dried, 608
 Tuberculin, 608, 609
 Tuberculosis, 294
 antibacterial prophylaxis, 295

Tuberculosis (*continued*)—
 diagnosis, 608
 immunisation
 vaccines, 608
 prophylaxis, 259
 travel, 632
 Tubular bandages, 572
 Tumour lysis syndrome, 421
Turbohaler
 Bricanyl, 139
 Oxis, 136
 Symbicort, 147
 Turner's syndrome, 383, 387, 388
Twinrix preparations, 613
Tylenol (co-codamol 30/500), 202
Typhex, 626
Typhim Vi, 626
 Typhoid
 fever, treatment, 249
 immunisation
 vaccines, **626**
 travel, 632
 TYR preparations, 817, 818
 Tyrosinaemia, 500, 817
 Tyrosine supplement, 815, 817
Tyrosine1000, 815

U
 Ubidecarenone, **502**
 Ubiquinone *see* Ubidecarenone,
502
Ucerax, 155
 Ulcerative colitis, 47
 Ulcerative gingivitis
 antibacterial treatment, 255,
 299
 mouthwashes, 553
 Ulcer-healing drugs, 40
 Ulcers
 aphthous, 549
 corneal, 524, 527
 duodenal, 40, 41
 gastric, 40, 41
 mouth, 549
 NSAID-associated, 41
 Ulipristal, **414**
Ultiva, 647
Ultra products
 gluten-free, 808, 809, 810
Ultrapbase, 559
Ultralanum Plain, 571
Ultraproct, 66
 Ultraviolet radiation, 588
 Umbilical granulomas, 587
 Undecenoates, **596**
Unguentum M, 559
Uniphyllin Continus, 141
Uniroid-HC, 66
Unisept, 601
 Unithiol, 31
Univer, 108
 Unlicensed medicines, 2, 6
 Urea, 558, 559, 560
 emollient with, 560
 hydrocortisone and lactic acid
 with, 567
 hydrocortisone with, 567

Urea cycle disorders, 498
essential amino acids
supplement, 815

Urethritis, non-gonococcal, 253, 277

Uriflex preparations, 418

Urinary
alkalinisation, 417
frequency, 415
incontinence, 415
infections, 303
genital, 400
prophylaxis, 259, 303
treatment, 252
retention, 414

Urine tests, 369, 372

Uristix, 372

Urokinase, **121**

Uro-Tainer preparations, 417, 418

Ursodeoxycholic acid, **68**

Ursofalk, 68

Ursogal, 68

Urticaria, 152

UT 380 devices, 413

Urovlan, 384

UVB, psoriasis, 574

Uvistat preparations, 589

V

Vaccination
HIV-positive subjects, 605
schedule, 606
travel, 632

Vaccines
active immunity, 604
allergen extract, 156
breast-feeding, 605
cautions, 604
contra-indications, 604
post-immunisation pyrexia, 605
pregnancy, 605
side-effects, 605
storage and use, 607

Vaginal infection
oral treatment, 398

Vaginitis
candidal, 399

Vaginosis, bacterial, 400

Vaginyll (metronidazole), 300

Valaciclovir, 326, **327**, 328
genito-urinary infection, 400
herpetic stomatitis, 551

Valine50, 815

Valni XL, 107

Valoid, 194
tablets—*discontinued*

Valproate
bipolar disorder, 181
epilepsy, 219, **231**, 232, 233

Valproic acid *see* Valproate

Valsartan, 101, **102**

Valtrex, 328

Vamin preparations, 473

Vaminolact, 473

Vancocin, 290

Vancomycin, 288, **289**, 290
eye, 536

Vancomycin-resistant enterococci, 290

Vaqta, 613

Variceal bleeding, 391

Varicella-zoster, 325, 326
corticosteroids, 377
immunisation
vaccine, **627**, 631
immunoglobulin, **631**, 632

Varilrix, 627

Variquel, 393

Varivax, 627

Vascular spasm, 104, **107**

Vasoconstrictors
local anaesthesia, 654
dental, 655
sympathomimetic, 110

Vasodilators
antihypertensive, 91
peripheral, 108

Vasopressin
shock, 109
variceal bleeding, 391, **393**

Vectavir, 597

Vecuronium, 648, **650**, 651
infusion table (neonatal), 825

Vedrop, 490

Vegenat-med preparations, 790

Veil preparations, 589

Velaglucerase alfa, 495, **496**

Velbe, 431

Venofer, 452

Venta-Neb, 95

Ventavis, 95

Ventmax SR, 137

Ventolin preparations, 137, 138

Vepesid, 431

Veracur, 586

Verapamil, **107**
arrhythmias, 81, 82, 104
beta-blockers and, 107
hypertension, 104
poisoning by, 29
see also Calcium-channel
blockers

Verapress MR, 108

Vermox, 353

Verrucas, 586

Verrugon, 586

Vertab SR 240, 108

Vertigo, 193

Vesanoïd, 435

Vestibular disorders, 193

Vfend, 309

ViATIM, 614

Vibramycin-D, 279

Victanyl (fentanyl), 208

Videne, 601

Videx preparations, 316

Vigabatrin, 219, **233**, 234

Vigam, 630

Vigranon-B, 486

Vilanterol
fluticasone with, 149

Vimpat, 224

Vinblastine, **431**

Vinca alkaloids, 430

Vincent's infection
antibacterial treatment, 255, 299
mouthwashes, 553

Vincristine, **431**, 432

Viper venom antiserum, European, 33

ViraféronPeg, 446

Viramune, 324

Virazole, 333

Viread preparations, 318

Viroflu, 617

Viormone, 385

Virus infections, 313

Visclair—*discontinued*

Viscotears preparations, 536

Vismed preparations, 538

Vistamethasone
ear, 542
eye, 528
nose, 546

Vita-Bite, 810

Vitaflo Choices, 810

Vitajoule, 801

Vitalograph, 142

Vitamin A, **484**
vitamin D and, **484**, 485

Vitamin B group, 485
preparations, 486

Vitamin B₁₂, 452, 453

Vitamin C *see* Ascorbic acid

Vitamin D, 487, 488
psoriasis, 573, 574

Vitamin D₂ *see* Ergocalciferol, 487, **488**

Vitamin D₃ *see* Colecalciferol

Vitamin deficiency, 484

Vitamin E, 490

Vitamin K, 491, 492
deficiency bleeding, 491
palliative care, 18

Vitamins, 484
children's drops, 485
multivitamins, **492**
parenteral, 474

Vita-POS, 537

Vitapro, 803

Vitaquick, 807

Vitasavoury, 806

Vitiligo, 589
ACBS, 819

Vitlipid N, 474

Vivadex, 443

Vividrin nasal spray—*discontinued*

Vividrin (sodium cromoglicate), 530

Vivotif, 626

Volplex, 472

Volsaid (diclofenac) preparations, 507

Voltarol preparations, 507
eye, 540
Ophtha, 540
Rapid, 506

Volulyte—*discontinued*

Volumatic, 143

Volume expansion, 471

Voluven—discontinued

Vomiting

- cytotoxic drugs, 420
- nausea and, 192
- opioid-induced, 193
- palliative care, 18
- postoperative, 193
- pregnancy, 193

von Willebrand's disease, **391**Voriconazole, 304, 305, **308**, 309

Vortex, 143

Votubia, 434

VPRIV, 496

Vulvitis, candidal, 398

Vulvovaginal candidiasis,
recurrent, 398VZIG *see* Immunoglobulins,
varicella–zoster, 631, 632

W

Warburtons products, 808, 809

Warfarin, **117**, 118

Warticon preparations, 587

Warts, 586

- anogenital, 587

Wasp sting allergy preparations,
156

Water for injections, 471

WaveSense products, 371

Waxsol, 545

Wellform, 169

Wellfoods products, 808, 809, 810

Wellvone, 351

West's syndrome, 233

Whitfield's ointment, 594

Whooping cough *see* Pertussis

Wilate (factor VIII fraction), 122

Wilson's disease, 493

Wilzin, 494

Withdrawal

- antipsychotics, 172
- nicotine, 242
- opioids, 205

Wolff-Parkinson-White syndrome,
81

Wool fat, hydrous, 559

Worm infestation, 352

Wuchereria bancrofti, 354

Wysoy, 796

X

Xagrid, 460

Xalatan, 533

Xaluprine, 429

Xanthine bronchodilators *see*

Theophylline

Xenical, 192

Xepin, 564

Xerostomia, 554

Xerotin, 555

XLEU preparations, 813

XLYS preparations, 811, 812, 813

XMET preparations, 812, 813

XMTVI preparations, 814

Xolair, 157

Xomolix, 195

XP preparations, 817

XPHEN TYR preparations, 818

XPTM preparations, 818

Xylitol, presence of, 3

Xylocaine, 657, 658

Xylometazoline

- eye, 529

- nose, **548**

Xyloproct, 66

Xyzal, 154

Y

8Y (factor VIII fraction), 122

Yasmin, 406

Yeasts, 309

Yellow cards

- adverse drug reporting, 11
- reporting cards, *inside back cover*

Yellow fever

- immunisation

- vaccine, **627**

- travel, 632

Z

Zaditen, 155, 529

Zafirlukast, 150, **151**

Zalasta (olanzapine), 179

Zamadol preparations (tramadol),
212, 213Zanamivir, 330, **332**

Zantac, 42

Zapain (co-codamol 30/500), 202

Zaponex, 179

Zarontin, 222

Zarzio, 462

Zavesca, 501

ZeaSORB, 602

Zeffix, 317

Zenalb preparations (albumin), 471

Zeridame SR (tramadol), 212

Zerit, 317

ZeroAQS, 559

Zerobase, 559

Zerocream, 559

Zeroguent, 559

Zerolatum preparations, 562

Zeroneum, 562

Zestril, 101

Ziagen, 315

Zicron (gliclazide), 365

Zidoval, 400

Zidovudine, 314, **318**, 319

- abacavir and lamivudine with,
316
- lamivudine with, 319

Zinacef, 275

Zinamide, 298

Zinc

- bandages, 572
- deficiency, **483**
- skin
 - castor oil and, 563
 - coal tar with, 576
 - cod liver oil with, 563
 - dimeticone with, 563
 - ichthammol with, 572, 573
 - salicylic acid with, 577
- Wilson's disease (zinc acetate), **494**

Zindaclin, 582

Zineryt, 582

Zinnat, 275

Zithromax, 285

Zocor, 126

Zofran, 198

Zoladex preparations, 386

Zollinger–Ellison syndrome, 43

Zolmitriptan

- cluster headache, **214**, 215
- migraine, 213, **214**, 215

Zolvera (verapamil), 108

Zomacton, 390

Zomig preparations, 215

Zonegran, 234

Zonisamide, 219, **234**Zoster *see* Herpes infections

Zoton FasTab, 44

Zovirax preparations, 327

- cold sore cream, 597
- cream, 597
- eye ointment, 527

Zydol preparations, 212, 213

Zyloric, 422

Zyomet, 594

Zyprexa, 179

Zyvox, 291

YellowCard

COMMISSION ON HUMAN MEDICINES (CHM)

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www.mhra.gov.uk/yellowcard

**REPORT OF SUSPECTED ADVERSE DRUG REACTIONS**

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See 'Adverse reactions to drugs' section in BNFC or www.mhra.gov.uk/yellowcard for guidance. Do not be put off reporting because some details are not known.

PATIENT DETAILS Patient Initials: _____ Sex: M / F Is the patient pregnant? Y / N Ethnicity: _____
 Age (at time of reaction): _____ Weight (kg): _____ Identification number (e.g. Practice or Hospital Ref): _____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

SUSPECTED REACTION(S) Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

Outcome

Recovered ☐
 Recovering ☐
 Continuing ☐
 Other ☐

Date reaction(s) started: _____ Date reaction(s) stopped: _____

Do you consider the reactions to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

☐ Patient died due to reaction ☐ Involved or prolonged inpatient hospitalisation
☐ Life threatening ☐ Involved persistent or significant disability or incapacity
☐ Congenital abnormality Medically significant; please give details: _____

If the reactions were not serious according to the categories above, how bad was the suspected reaction?

☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities

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OTHER DRUG(S) (including self-medication and complementary remedies)

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS

Name and Professional Address: _____

Postcode: _____ Tel No: _____

Email: _____

Speciality: _____

Signature: _____ Date: _____

CLINICIAN (if not the reporter)

Name and Professional Address: _____

Postcode: _____ Tel No: _____

Email: _____

Speciality: _____

Date: _____

Information on adverse drug reactions received by the MHRA can be downloaded at www.mhra.gov.uk/daps

Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin *Drug Safety Update* at: www.mhra.gov.uk/drugsafetyupdate

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)

YellowCard

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 Age (at time of reaction): _____ Weight (kg): _____ Identification number (e.g. Practice or Hospital Ref): _____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

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Outcome

Recovered ☐
 Recovering ☐
 Continuing ☐
 Other ☐

Date reaction(s) started: _____ Date reaction(s) stopped: _____

Do you consider the reactions to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

- | | |
|---|--|
| <input type="checkbox"/> Patient died due to reaction | <input type="checkbox"/> Involved or prolonged inpatient hospitalisation |
| <input type="checkbox"/> Life threatening | <input type="checkbox"/> Involved persistent or significant disability or incapacity |
| <input type="checkbox"/> Congenital abnormality | Medically significant; please give details: _____ |

If the reactions were not serious according to the categories above, how bad was the suspected reaction?

- ☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities

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OTHER DRUG(S) (including self-medication and complementary remedies)

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

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PATIENT DETAILS Patient Initials: _____ Sex: M / F Is the patient pregnant? Y / N Ethnicity: _____
 Age (at time of reaction): _____ Weight (kg): _____ Identification number (e.g. Practice or Hospital Ref): _____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

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 Recovering ☐
 Continuing ☐
 Other ☐

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Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS

Name and Professional Address: _____

Postcode: _____ Tel No: _____

Email: _____

Speciality: _____

Signature: _____ Date: _____

CLINICIAN (if not the reporter)

Name and Professional Address: _____

Postcode: _____ Tel No: _____

Email: _____

Speciality: _____

Date: _____

Information on adverse drug reactions received by the MHRA can be downloaded at www.mhra.gov.uk/daps

Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin *Drug Safety Update* at: www.mhra.gov.uk/drugsafetyupdate

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)

YellowCard

COMMISSION ON HUMAN MEDICINES (CHM)

It's easy to report online at:
www.mhra.gov.uk/yellowcard

**REPORT OF SUSPECTED ADVERSE DRUG REACTIONS**

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See 'Adverse reactions to drugs' section in BNFC or www.mhra.gov.uk/yellowcard for guidance. Do not be put off reporting because some details are not known.

PATIENT DETAILS Patient Initials: _____ Sex: M / F Is the patient pregnant? Y / N Ethnicity: _____
 Age (at time of reaction): _____ Weight (kg): _____ Identification number (e.g. Practice or Hospital Ref): _____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

SUSPECTED REACTION(S) Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

Outcome

Recovered ☐
 Recovering ☐
 Continuing ☐
 Other ☐

Date reaction(s) started: _____ Date reaction(s) stopped: _____

Do you consider the reactions to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

☐ Patient died due to reaction ☐ Involved or prolonged inpatient hospitalisation
☐ Life threatening ☐ Involved persistent or significant disability or incapacity
☐ Congenital abnormality Medically significant; please give details: _____

If the reactions were not serious according to the categories above, how bad was the suspected reaction?

☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities

It's easy to report online: www.mhra.gov.uk/yellowcard

OTHER DRUG(S) (including self-medication and complementary remedies)

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____	_____

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS

Name and Professional Address: _____

Postcode: _____ Tel No: _____

Email: _____

Speciality: _____

Signature: _____ Date: _____

CLINICIAN (if not the reporter)

Name and Professional Address: _____

Postcode: _____ Tel No: _____

Email: _____

Speciality: _____

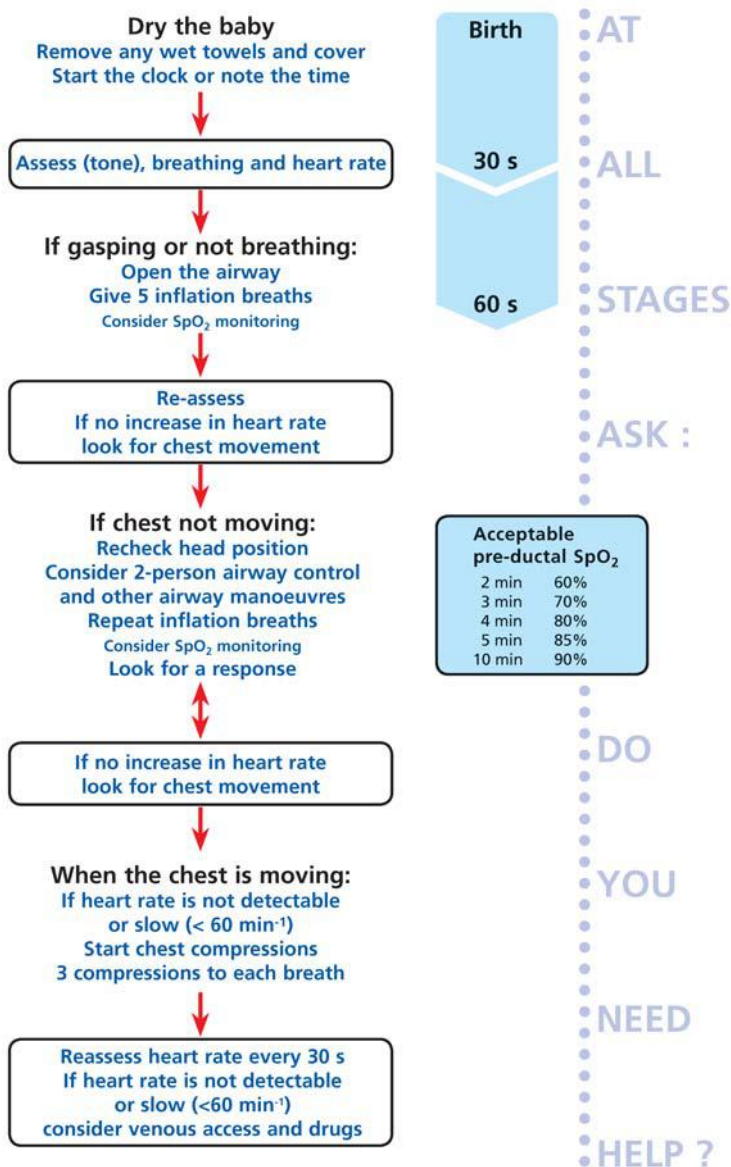
Date: _____

Information on adverse drug reactions received by the MHRA can be downloaded at www.mhra.gov.uk/daps

Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin *Drug Safety Update* at: www.mhra.gov.uk/drugsafetyupdate

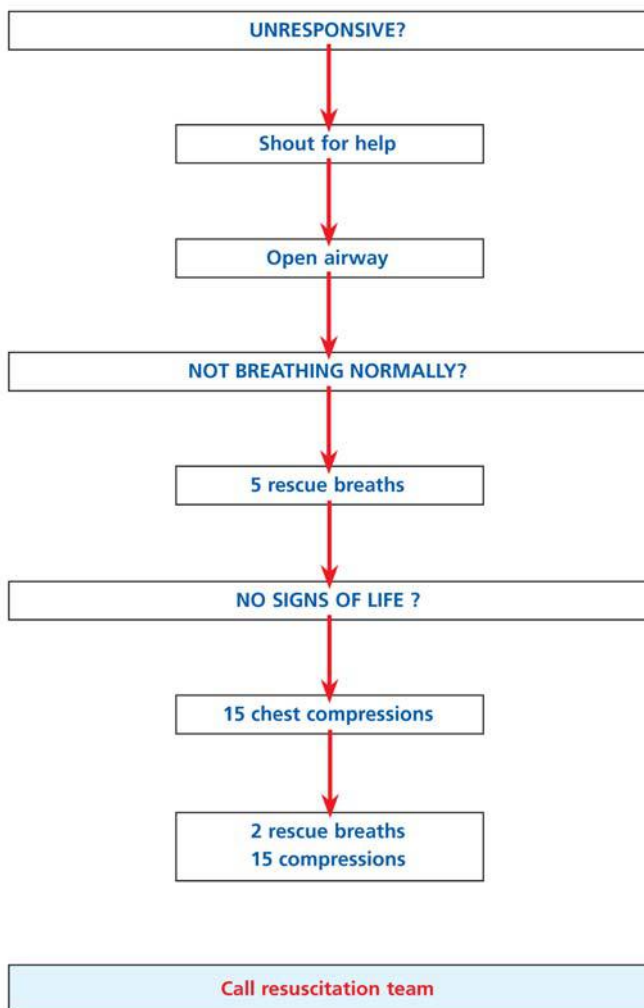
Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)

NEWBORN LIFE SUPPORT



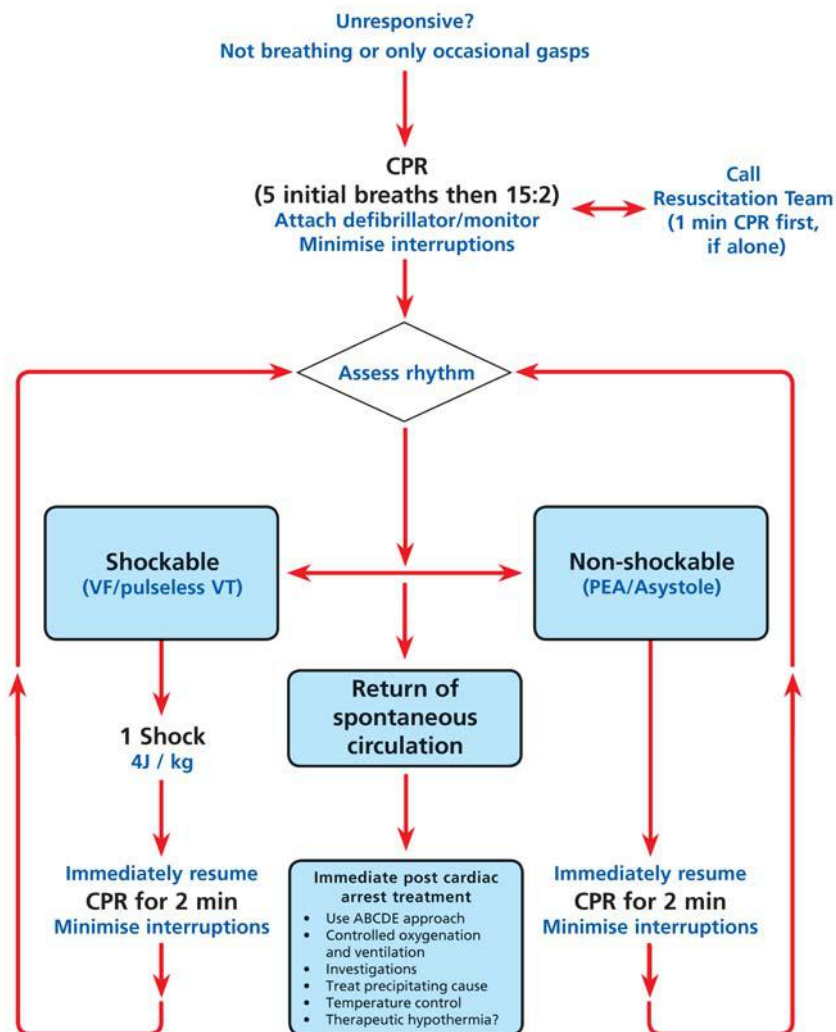
PAEDIATRIC BASIC LIFE SUPPORT

(Healthcare professionals with a duty to respond)



Resuscitation Council (UK)

PAEDIATRIC ADVANCED LIFE SUPPORT



During CPR

- Ensure high-quality CPR: rate, depth, recoil
- Plan actions before interrupting CPR
- Give oxygen
- Vascular access (intravenous, intraosseous)
- Give adrenaline every 3-5 min
- Consider advanced airway and capnography
- Continuous chest compressions when advanced airway in place
- Correct reversible causes

Reversible causes

- Hypoxia
- Hypovolaemia
- Hypo- / hyperkalaemia / metabolic
- Hypothermia
- Tension pneumothorax
- Toxins
- Tamponade - cardiac
- Thromboembolism



Resuscitation Council (UK)

BODY SURFACE AREA IN CHILDREN

Body-weight under 40kg

Body-weight (kg)	Surface area (m ²)
1	0.10
1.5	0.13
2	0.16
2.5	0.19
3	0.21
3.5	0.24
4	0.26
4.5	0.28
5	0.30
5.5	0.32
6	0.34
6.5	0.36
7	0.38
7.5	0.40
8	0.42
8.5	0.44
9	0.46
9.5	0.47
10	0.49
11	0.53
12	0.56
13	0.59
14	0.62
15	0.65
16	0.68

Body-weight (kg)	Surface area (m ²)
17	0.71
18	0.74
19	0.77
20	0.79
21	0.82
22	0.85
23	0.87
24	0.90
25	0.92
26	0.95
27	0.97
28	1.0
29	1.0
30	1.1
31	1.1
32	1.1
33	1.1
34	1.1
35	1.2
36	1.2
37	1.2
38	1.2
39	1.3
40	1.3

Values are calculated using the Boyd equation

Note Height is not required to estimate body surface area using these tables

BODY SURFACE AREA IN CHILDREN

Body-weight over 40kg

Body-weight (kg)	Surface area (m ²)
41	1.3
42	1.3
43	1.3
44	1.4
45	1.4
46	1.4
47	1.4
48	1.4
49	1.5
50	1.5
51	1.5
52	1.5
53	1.5
54	1.6
55	1.6
56	1.6
57	1.6
58	1.6
59	1.7
60	1.7
61	1.7
62	1.7
63	1.7
64	1.7
65	1.8

Body-weight (kg)	Surface area (m ²)
66	1.8
67	1.8
68	1.8
69	1.8
70	1.9
71	1.9
72	1.9
73	1.9
74	1.9
75	1.9
76	2.0
77	2.0
78	2.0
79	2.0
80	2.0
81	2.0
82	2.1
83	2.1
84	2.1
85	2.1
86	2.1
87	2.1
88	2.2
89	2.2
90	2.2

Values are calculated using the Boyd equation

Note Height is not required to estimate body surface area using these tables

Medical emergencies in the community

Drug treatment outlined below is intended for use by appropriately qualified healthcare professionals. Only drugs that are used for immediate relief are shown; advice on supporting care is not given. Where the child's condition requires investigation and further treatment, the child should be transferred to hospital promptly.

Anaphylaxis

(section 3.4.3)

Adrenaline injection (1 mg/mL (1 in 1000))

- By intramuscular injection
Child under 6 years 150 micrograms (0.15 mL), repeated every 5 minutes if necessary
Child 6–12 years 300 micrograms (0.3 mL), repeated every 5 minutes if necessary
Child 12–18 years 500 micrograms (0.5 mL), repeated every 5 minutes if necessary; 300 micrograms (0.3 mL) should be given if child is small or prepubertal

High-flow **oxygen** (section 3.6) and **intravenous fluids** should be given as soon as available.

Chlorphenamine injection by intramuscular or intravenous injection (section 3.4.1) may help counter histamine-mediated vasodilation and bronchoconstriction.

Hydrocortisone (preferably as sodium succinate) by intravenous injection (section 6.3.2) has delayed action but it should be given to severely affected children to prevent further deterioration.

Asthma: acute

(section 3.1)

Regard each emergency consultation as being for **severe acute asthma** until shown otherwise; failure to respond adequately **at any time** requires immediate transfer to hospital

Either salbutamol aerosol inhaler (100 micrograms/metered inhalation)

- By aerosol inhalation via large-volume spacer (and a close-fitting face mask if child under 3 years)
Child under 18 years 2–10 puffs each inhaled separately, repeated at 10–20 minute intervals or as necessary

or salbutamol nebuliser solution (1 mg/mL, 2 mg/mL)

- By inhalation of nebulised solution (via oxygen-driven nebuliser if available)
Child under 5 years 2.5 mg every 20–30 minutes or as necessary
Child 5–12 years 2.5–5 mg every 20–30 minutes or as necessary
Child 12–18 years 5 mg every 20–30 minutes or as necessary

or terbutaline nebulised solution (2.5 mg/mL)

- By inhalation of nebulised solution (via oxygen-driven nebuliser if available)
Child under 5 years 5 mg every 20–30 minutes or as necessary

Child 5–12 years 5–10 mg every 20–30 minutes or as necessary

Child 12–18 years 10 mg every 20–30 minutes or as necessary

Plus (in all cases)

Either prednisolone tablets (or prednisolone soluble tablets) (5 mg)

- By mouth
Child under 12 years 1–2 mg/kg (max. 40 mg) once daily for up to 3 days or longer if necessary; if the child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (max. 60 mg) once daily
Child 12–18 years 40–50 mg once daily for at least 5 days

or hydrocortisone (preferably as sodium succinate)

- By intravenous injection
Child up to 18 years 4 mg/kg (max. 100 mg) every 6 hours, until conversion to oral prednisolone is possible; alternative dose if weight unavailable,
Child under 2 years 25 mg, **2–5 years** 50 mg, **5–18 years** 100 mg

High-flow **oxygen** (section 3.6) should be given if available (via face mask)

Monitor response 15 to 30 minutes after nebulisation; if any signs of acute asthma persist, arrange hospital admission. While awaiting ambulance, repeat **nebulised beta₂ agonist** (as above) and give with

ipratropium nebuliser solution (250 micrograms/mL)

- By inhalation of nebulised solution (via oxygen-driven nebuliser if available)
Child under 12 years 250 micrograms repeated every 20–30 minutes for the first 2 hours, then every 4–6 hours as necessary
Child 12–18 years 500 micrograms every 4–6 hours as necessary

Convulsive (including febrile) seizures lasting longer than 5 minutes

(section 4.8.2 and section 4.8.3)

Midazolam buccal solution

- By buccal administration, repeated once after 10 minutes if necessary
Neonate 300 micrograms/kg
Child 1–3 months 300 micrograms/kg (max. 2.5 mg)
Child 3 months–1 year 2.5 mg
Child 1–5 years 5 mg
Child 5–10 years 7.5 mg
Child 10–18 years 10 mg

or diazepam rectal solution (2 mg/mL, 4 mg/mL)

- By rectum, repeated once after 10 minutes if necessary
Neonate 1.25–2.5 mg
Child 1 month–2 years 5 mg
Child 2–12 years 5–10 mg
Child 12–18 years 10–20 mg

Croup

(section 3.1)

Dexamethasone oral solution (2 mg/5 mL)

- By mouth
Child 1 month–2 years 150 micrograms/kg as a single dose

Diabetic hypoglycaemia

(section 6.1.4)

Glucose or sucrose

- By mouth
Child 2–18 years approx. 10–20 g (55–110 mL *Lucozade® Energy Original* or 100–200 mL *Coca-Cola®*—both non-diet versions or 2–4 teaspoonfuls of sugar or 3–6 sugar lumps), repeated after 10–15 minutes if necessary

or if hypoglycaemia unresponsive or if oral route cannot be used

Glucagon injection (1 mg/mL)

- By subcutaneous, intramuscular or intravenous injection
Child body-weight under 25 kg 500 micrograms (0.5 mL)
Child body-weight over 25 kg 1 mg (1 mL)

or if hypoglycaemia prolonged or unresponsive to glucagon after 10 minutes

Glucose intravenous infusion (10%)

- By intravenous injection into large vein
Child 1 month–18 years 5 mL/kg (glucose 500 mg/kg)

Meningococcal disease

(Table 1, section 5.1)

Benzylpenicillin sodium injection (600 mg, 1.2 g)

- By intravenous injection (or by intramuscular injection if venous access not available)
Neonate 300 mg
Child 1 month–1 year 300 mg
Child 1–10 years 600 mg
Child 10–18 years 1.2 g

Note A single dose should be given before urgent transfer to hospital, so long as this does not delay the transfer

or if history of allergy to penicillin

Cefotaxime injection (1 g)

- By intravenous injection (or by intramuscular injection if venous access not available)
Neonate 50 mg/kg
Child 1 month–12 years 50 mg/kg (max. 1 g)
Child 12–18 years 1 g

Note A single dose can be given before urgent transfer to hospital, so long as this does not delay the transfer

or if history of immediate hypersensitivity reaction (including anaphylaxis, angioedema, urticaria, or rash immediately after administration) to penicillin or to cephalosporins

Chloramphenicol injection (1 g)

- By intravenous injection
Child 1 month–18 years 12.5–25 mg/kg
Note A single dose can be given before urgent transfer to hospital, so long as this does not delay the transfer

Approximate conversions and units

lb	kg	stones	kg	mL	fl oz
1	0.45	1	6.35	50	1.8
2	0.91	2	12.70	100	3.5
3	1.36	3	19.05	150	5.3
4	1.81	4	25.40	200	7.0
5	2.27	5	31.75	500	17.6
6	2.72	6	38.10	1000	35.2
7	3.18	7	44.45		
8	3.63	8	50.80		
9	4.08	9	57.15		
10	4.54	10	63.50		
11	4.99	11	69.85		
12	5.44	12	76.20		
13	5.90	13	82.55		
14	6.35	14	88.90		
		15	95.25		

Length

1 metre (m)	= 1000 millimetres (mm)
1 centimetre (cm)	= 10 mm
1 inch (in)	= 25.4 mm
1 foot (ft)	= 12 inches
12 inches	= 304.8 mm

Mass

1 kilogram (kg)	= 1000 grams (g)
1 gram (g)	= 1000 milligrams (mg)
1 milligram (mg)	= 1000 micrograms
1 microgram	= 1000 nanograms
1 nanogram	= 1000 picograms

Volume

1 litre	= 1000 millilitres (mL)
1 millilitre (1 mL)	= 1000 microlitres
1 pint	≈ 568 mL

Other units

1 kilocalorie (kcal)	= 4186.8 joules (J)
1000 kilocalories (kcal)	= 4.1868 megajoules (MJ)
1 megajoule (MJ)	= 238.8 kilocalories (kcal)
1 millimetre of mercury (mmHg)	= 133.3 pascals (Pa)
1 kilopascal (kPa)	= 7.5 mmHg (pressure)

Plasma-drug concentrations in *BNF for Children* are expressed in mass units per litre (e.g. mg/litre). The approximate equivalent in terms of amount of substance units (e.g. micromol/litre) is given in brackets.

Prescribing for children

Weight, height, and gender

The table below shows the **mean values** for weight, height and gender by age; these values have been derived from the UK-WHO growth charts 2009 and UK1990 standard centile charts, by extrapolating the 50th centile, and may be used to calculate doses in the absence of actual measurements. However, the child's actual weight and height might vary considerably from the values in the table and it is important to see the child to ensure that the value chosen is appropriate. In most cases the child's actual measurement should be obtained as soon as possible and the dose re-calculated.

Age	Weight kg	Height cm
Full term neonate	3.5	51
1 month	4.3	55
2 months	5.4	58
3 months	6.1	61
4 months	6.7	63
6 months	7.6	67
1 year	9	75
3 years	14	96
5 years	18	109
7 years	23	122
10 years	32	138
12 years	39	149
14 year-old boy	49	163
14 year-old girl	50	159
Adult male	68	176
Adult female	58	164







Recommended wording of cautionary and advisory labels


For details see Appendix 3

1. Warning: This medicine may make you sleepy
2. Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines. Do not drink alcohol
3. Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines
4. Warning: Do not drink alcohol
5. Do not take indigestion remedies 2 hours before or after you take this medicine
6. Do not take indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine
7. Do not take milk, indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine
8. Warning: Do not stop taking this medicine unless your doctor tells you to stop
9. Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop
10. Warning: Read the additional information given with this medicine
11. Protect your skin from sunlight—even on a bright but cloudy day. Do not use sunbeds
12. Do not take anything containing aspirin while taking this medicine
13. Dissolve or mix with water before taking
14. This medicine may colour your urine. This is harmless
15. Caution: flammable. Keep your body away from fire or flames after you have put on the medicine
16. Dissolve the tablet under your tongue—do not swallow. Store the tablets in this bottle with the cap tightly closed. Get a new supply 8 weeks after opening
17. Do not take more than... in 24 hours
18. Do not take more than... in 24 hours. Also, do not take more than... in any one week
19. Warning: This medicine makes you sleepy. If you still feel sleepy the next day, do not drive or use tools or machines. Do not drink alcohol
21. Take with or just after food, or a meal
22. Take 30 to 60 minutes before food
23. Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food
24. Suck or chew this medicine
25. Swallow this medicine whole. Do not chew or crush
26. Dissolve this medicine under your tongue
27. Take with a full glass of water
28. Spread thinly on the affected skin only
29. Do not take more than 2 at any one time. Do not take more than 8 in 24 hours
30. Contains paracetamol. Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine, even if you feel well
32. Contains aspirin. Do not take anything else containing aspirin while taking this medicine

Abbreviations and symbols

Internationally recognised units and symbols are used in the *BNF for Children* where possible.

ACBS	Advisory Committee on Borderline Substances, see Appendix 2
ACE	Angiotensin-converting enzyme
ADHD	attention deficit hyperactivity disorder
AIDS	Acquired immunodeficiency syndrome
approx.	approximately
AV	atrioventricular
BAN	British Approved Name
BMI	body mass index
BP	British Pharmacopoeia 2013, unless otherwise stated
BPC	British Pharmaceutical Codex 1973 and Supplement 1976, unless otherwise stated
CAPD	Continuous ambulatory peritoneal dialysis
 C02	preparation in Schedule 2 of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Prescribing Controlled Drugs
 C03	preparation in Schedule 3 of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Prescribing Controlled Drugs
 C04-1	preparation in Schedule 4 (Part I) of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Prescribing Controlled Drugs
 C04-2	preparation in Schedule 4 (Part II) of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Prescribing Controlled Drugs
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
CSM	Committee on Safety of Medicines (now subsumed under Commission on Human Medicines)
d. c.	direct current
DMARD	Disease-modifying antirheumatic drug
DPF	Dental Practitioners' Formulary
e/c	enteric-coated (termed gastro-resistant in BP)
ECG	electrocardiogram
EEG	electro-encephalogram
f/c	film-coated
G6PD	glucose 6-phosphate dehydrogenase
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
i/m	intramuscular
i/v	intravenous
INR	international normalised ratio
MAOI	Monoamine-oxidase inhibitors
max.	maximum
MHRA	Medicines and Healthcare products Regulatory Agency
m/r	modified-release
NCL	no cautionary labels, see Appendix 3
NHS	National Health Service
 NHS	not prescribable under National Health Service (NHS)
NICE	National Institute for Health and Care Excellence
NPF	Nurse Prescribers' Formulary
NSAID	non-steroidal anti-inflammatory drug
PGD	patient group direction
PHE	Public Health England (formerly Health Protection Agency (HPA))
 PoM	prescription-only medicine, see Fig. 1, How to use <i>BNF for Children</i>
®	trade mark
rINN	Recommended International Non-proprietary Name
RSV	respiratory syncytial virus
s/c	sugar-coated

SLS	Selected List Scheme
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
spp.	species
SSRI	Selective serotonin reuptake inhibitors
UK	United Kingdom
Units	for SI units see Prescription Writing
WHO	World Health Organization
▼	limited experience of the use of this product and the MHRA requests that all suspected adverse reactions should be reported, see Adverse Reactions to Drugs
	considered by the Paediatric Formulary Committee to be less suitable for prescribing, see Fig. 1, How to use <i>BNF for Children</i>

Latin abbreviations

Directions should be in English without abbreviation. However, Latin abbreviations have been used when prescribing. The following is a list of appropriate abbreviations. It should be noted that the English version is not always an exact translation.

a. c.	= ante cibum (before food)
b. d.	= bis die (twice daily)
o. d.	= omni die (every day)
o. m.	= omni mane (every morning)
o. n.	= omni nocte (every night)
p. c.	= post cibum (after food)
p. r. n.	= pro re nata (when required)
q. d. s.	= quater die sumendum (to be taken four times daily)
q. q. h.	= quarta quaque hora (every four hours)
stat	= immediately
t. d. s.	= ter die sumendum (to be taken three times daily)
t.i.d.	= ter in die (three times daily)

E numbers

The following is a list of common E numbers and the inactive ingredients to which they correspond.

E102 Tartrazine	E211 Sodium Benzoate
E104 Quinoline Yellow	E223 Sodium Metabisulphite
E110 Sunset Yellow FCF	E320 Butylated Hydroxyanisole
E123 Amaranth	E321 Butylated Hydroxytoluene
E124 Ponceau 4R	E322 Lecithins
E127 Erythrosine BS	E420 Sorbitol
E132 Indigo Carmine	E421 Mannitol
E142 Green S	E422 Glycerol
E171 Titanium Dioxide	E901 Beeswax (white and yellow)
E172 Iron oxides, Iron hydroxides	E1520 Propylene Glycol
E200 Sorbic Acid	